

Rule-based modeling

Part I

Computational Biology 1 & 2

FDV 2009-2010

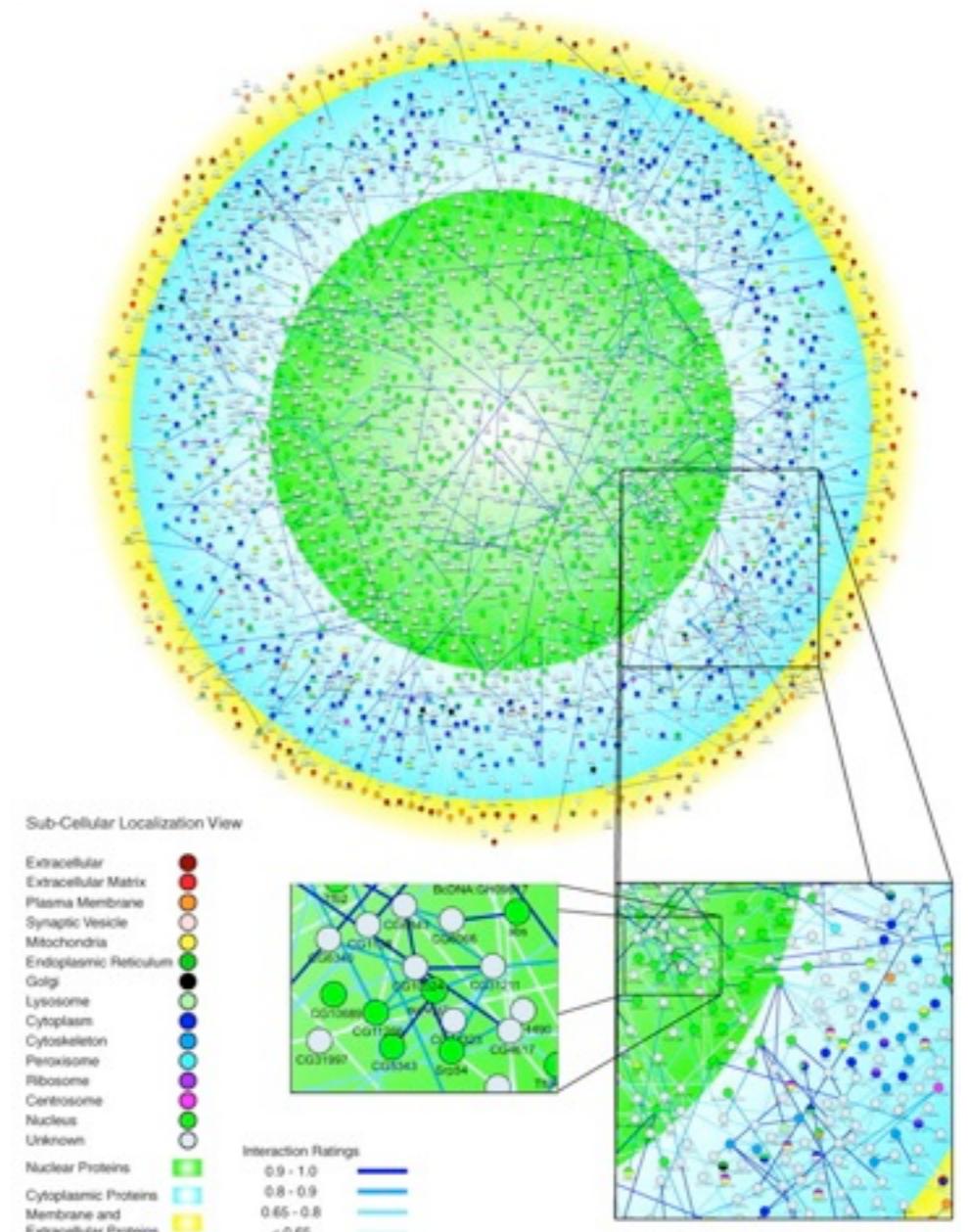
Large networks

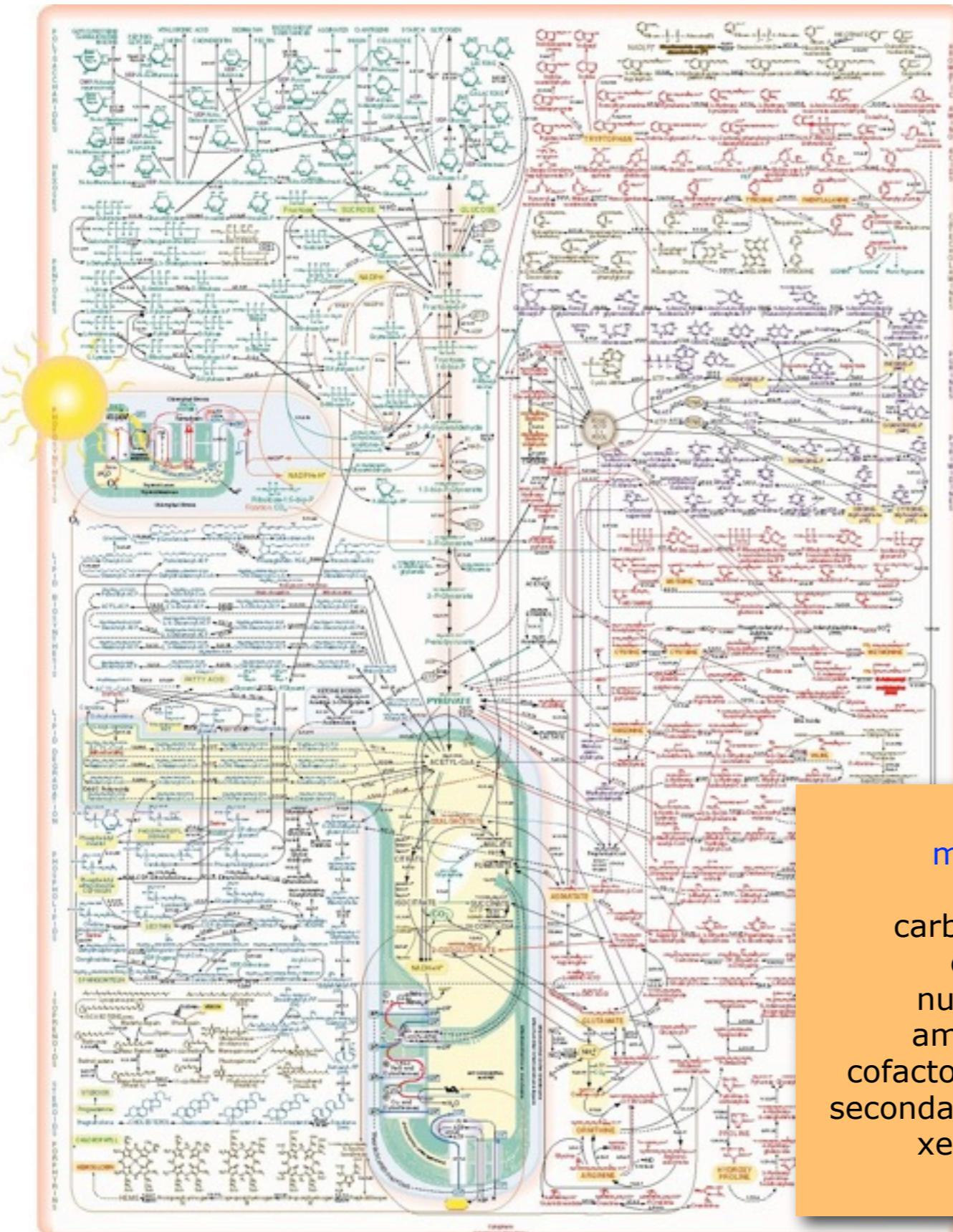
A panoramic view

How do we know about them?

What do they look like statically?

How to model their dynamical behavior?



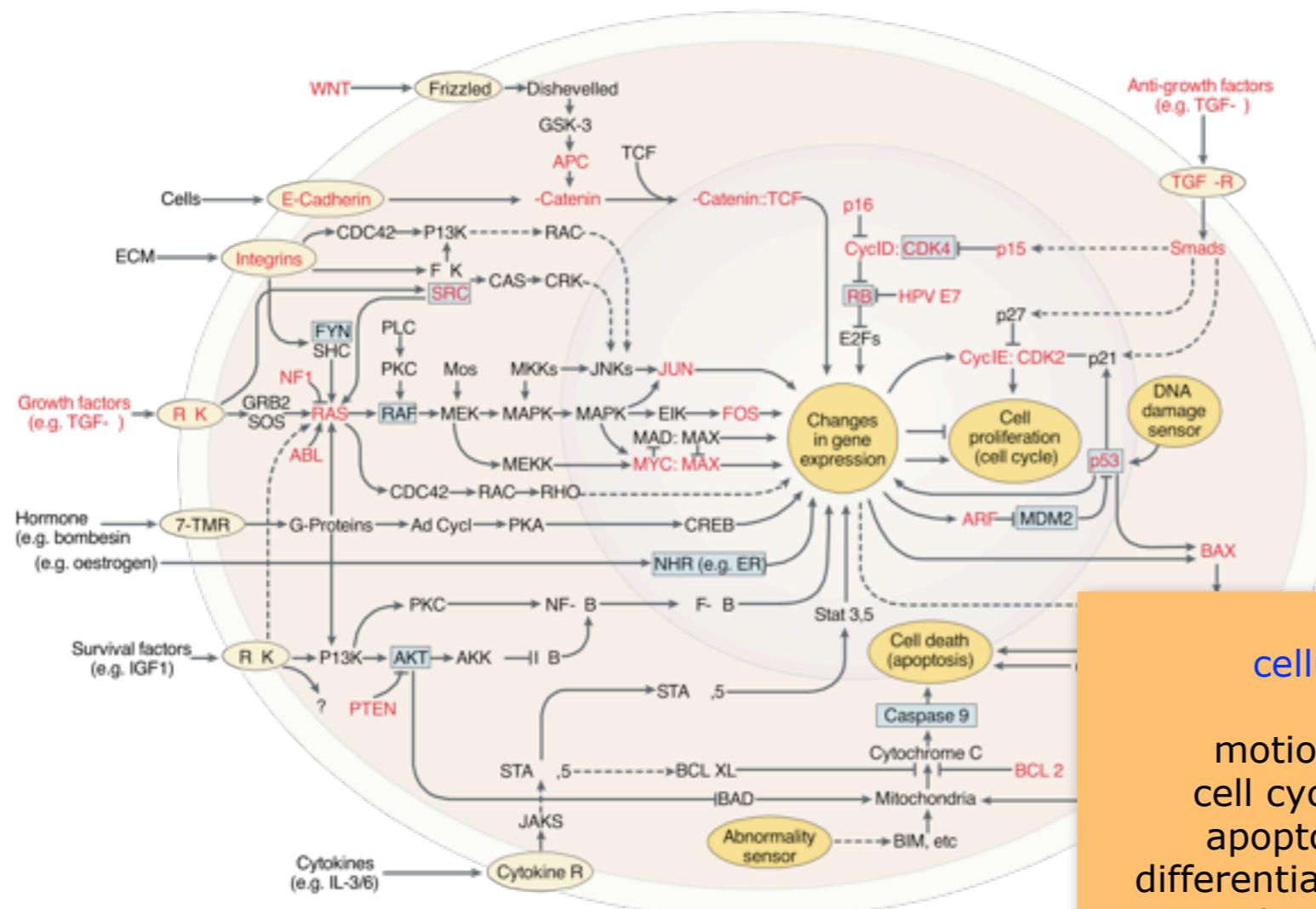


specialized enzymes transform substrates
(synthesis and break-down)

network flows are highly adaptive, but network
structure is constrained by chemistry

materials

carbohydrates
energy
nucleotides
amino acids
cofactors & vitamins
secondary metabolites
xenobiotics



No major chemical transformations.
Proteins modify the state of other proteins.
Communication is by physical contact.

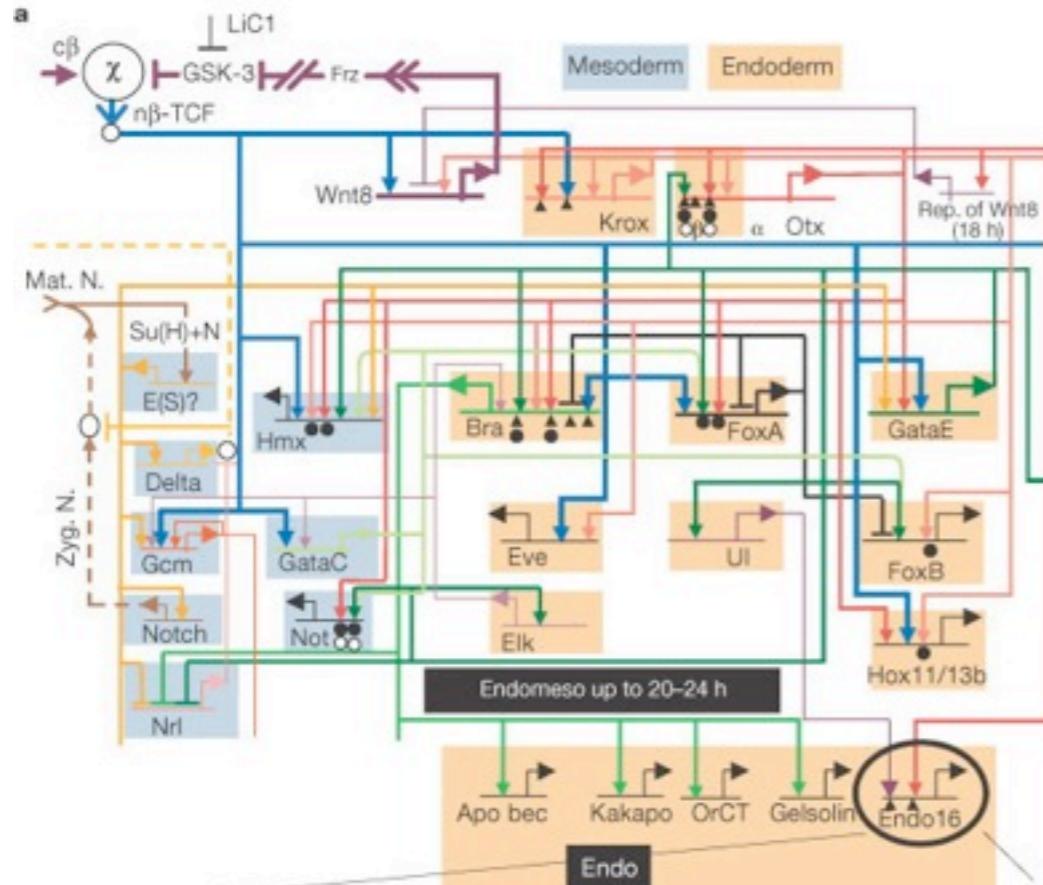
Network structure is reconfigurable.

cellular behavior

- motion (chemotaxis)
- cell cycle (cell division)
- apoptosis (cell death)
- differentiation (development)
- circadian rhythms
- cell adhesion
- transport
- repair
- transcription/translation
- maintenance

gene regulatory networks...

??



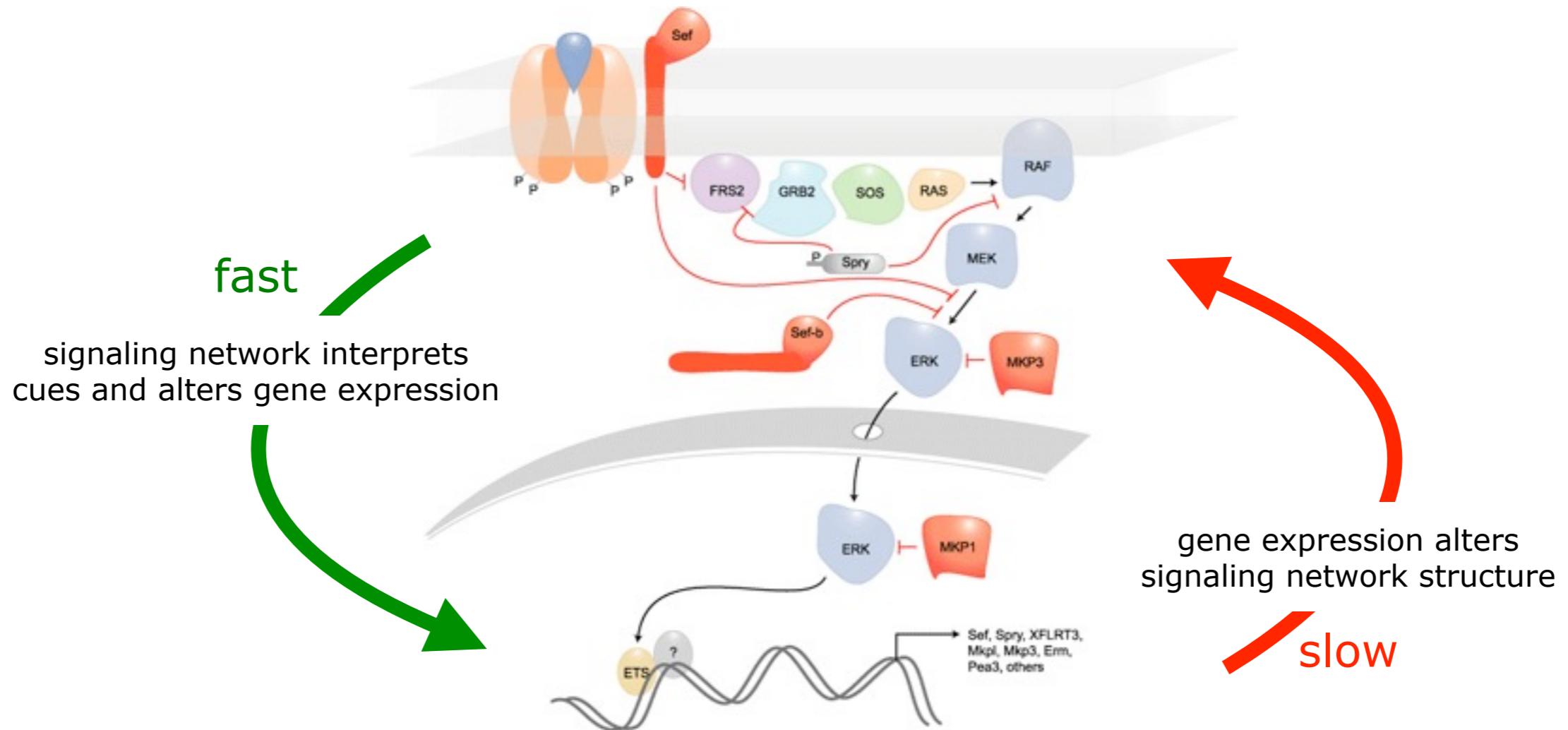
...also known as transcription networks,
in which transcription factors control the
expression of other transcription factors.

...mostly a projection, since “interactions between
genes” are mediated by interactions that occur as
part of signaling pathways.

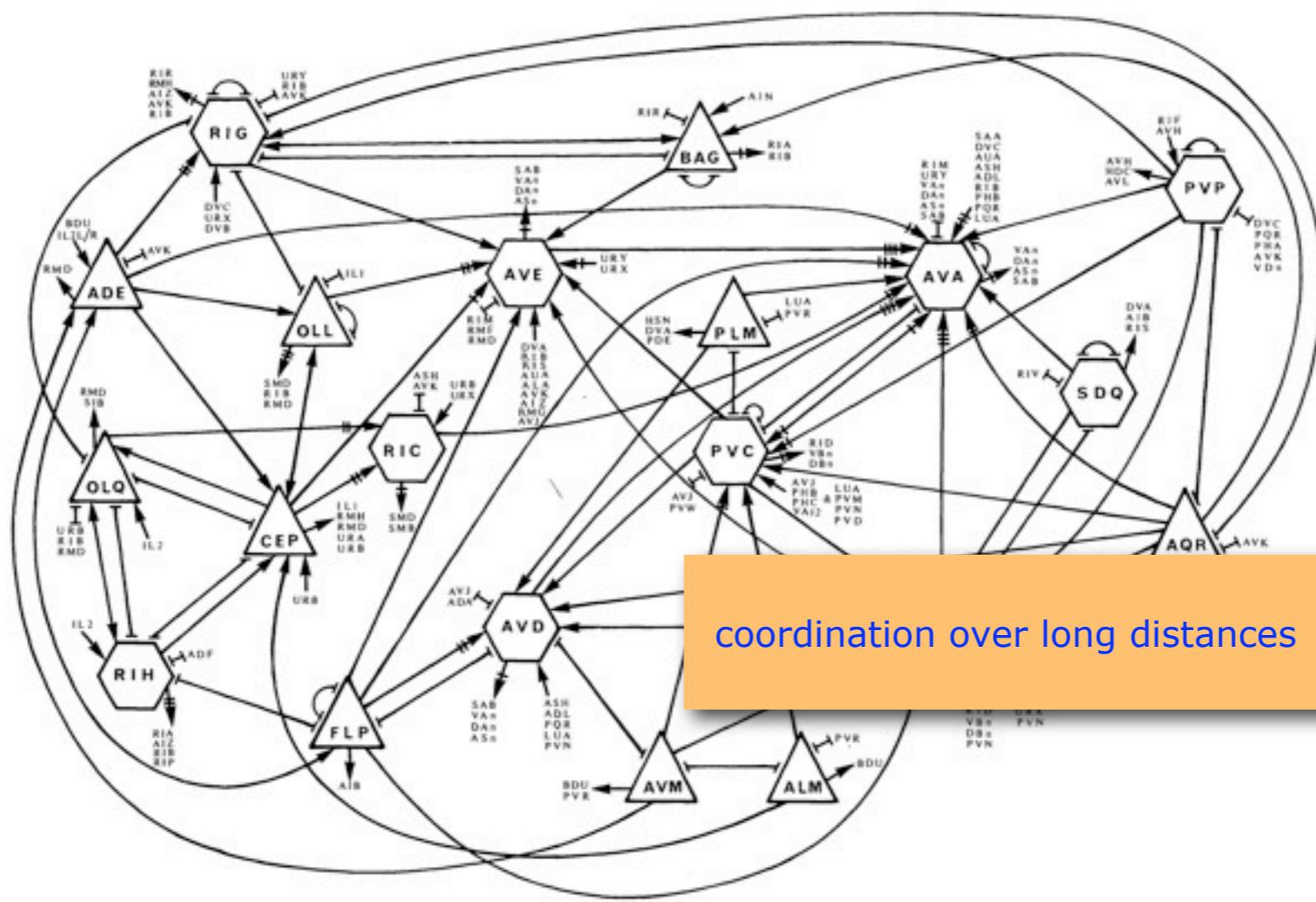
time scales in intra-cellular networks

learning?

completely under-explored!



Cells connect to cells in potentially arbitrary point-to-point contacts.
Network structure is extremely plastic.
(Network structure might be constrained by packing the wires.)



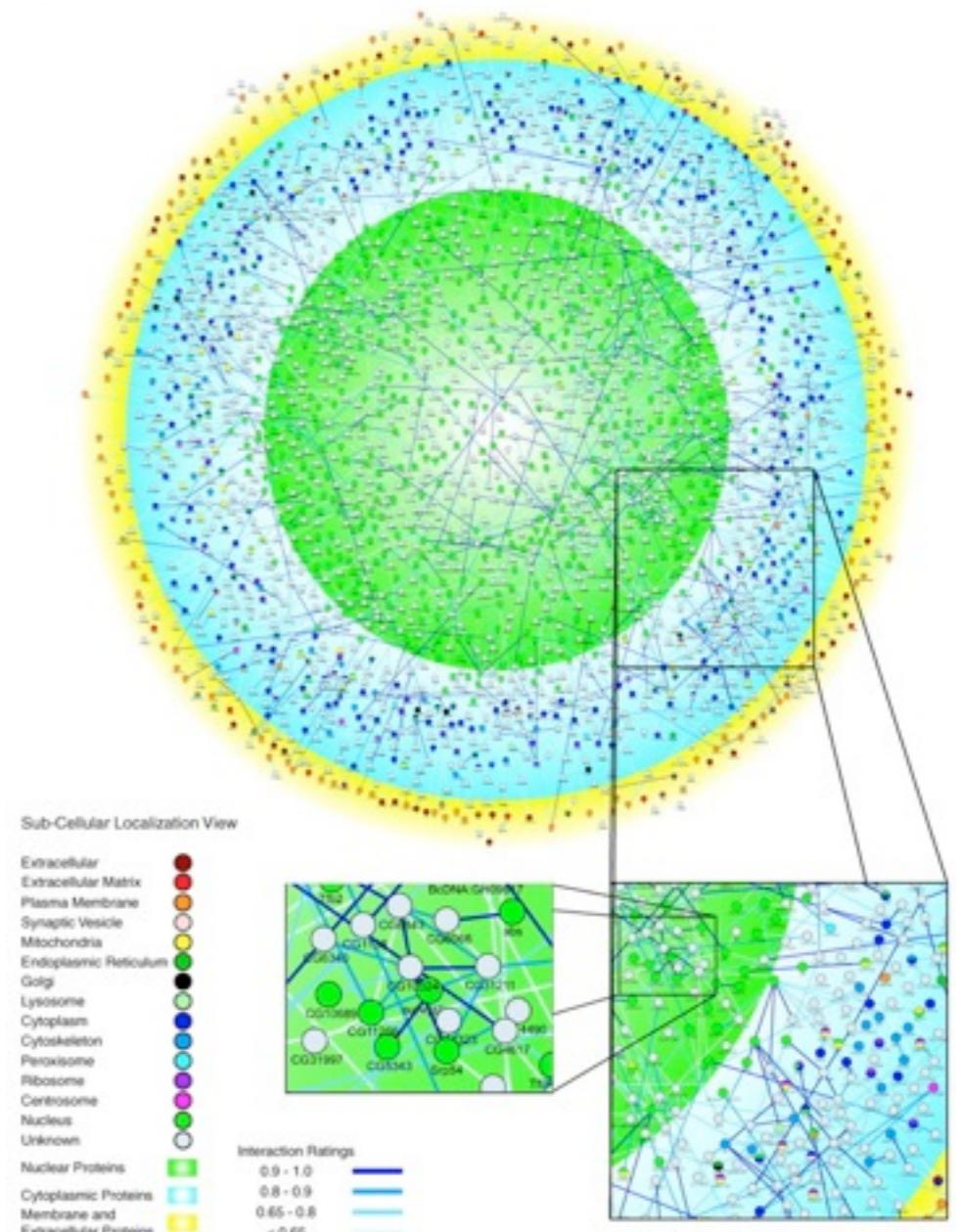
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How to build a network?

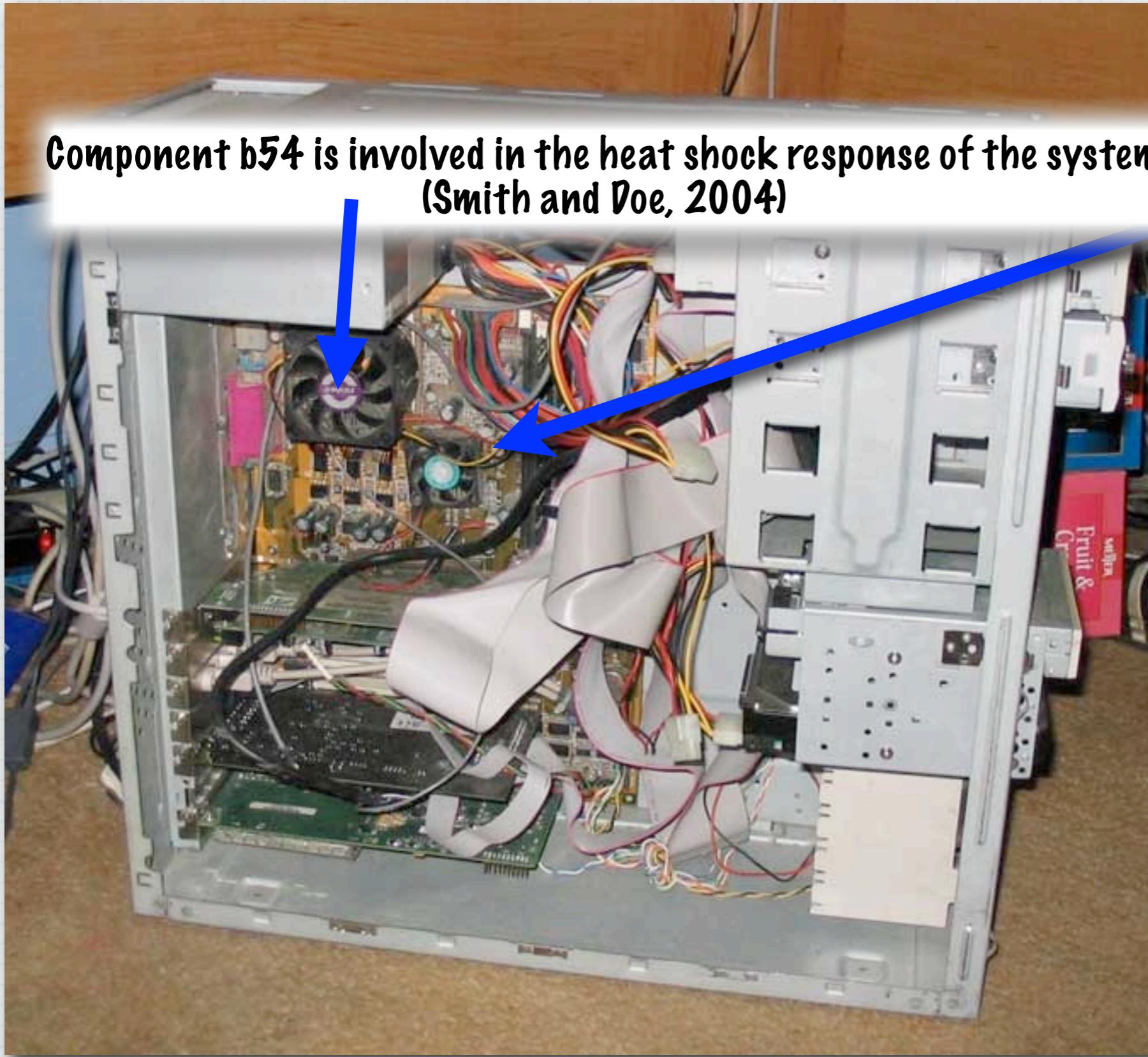


How to build a network?

Component b54 is involved in the heat shock response of the system
(Smith and Doe, 2004)



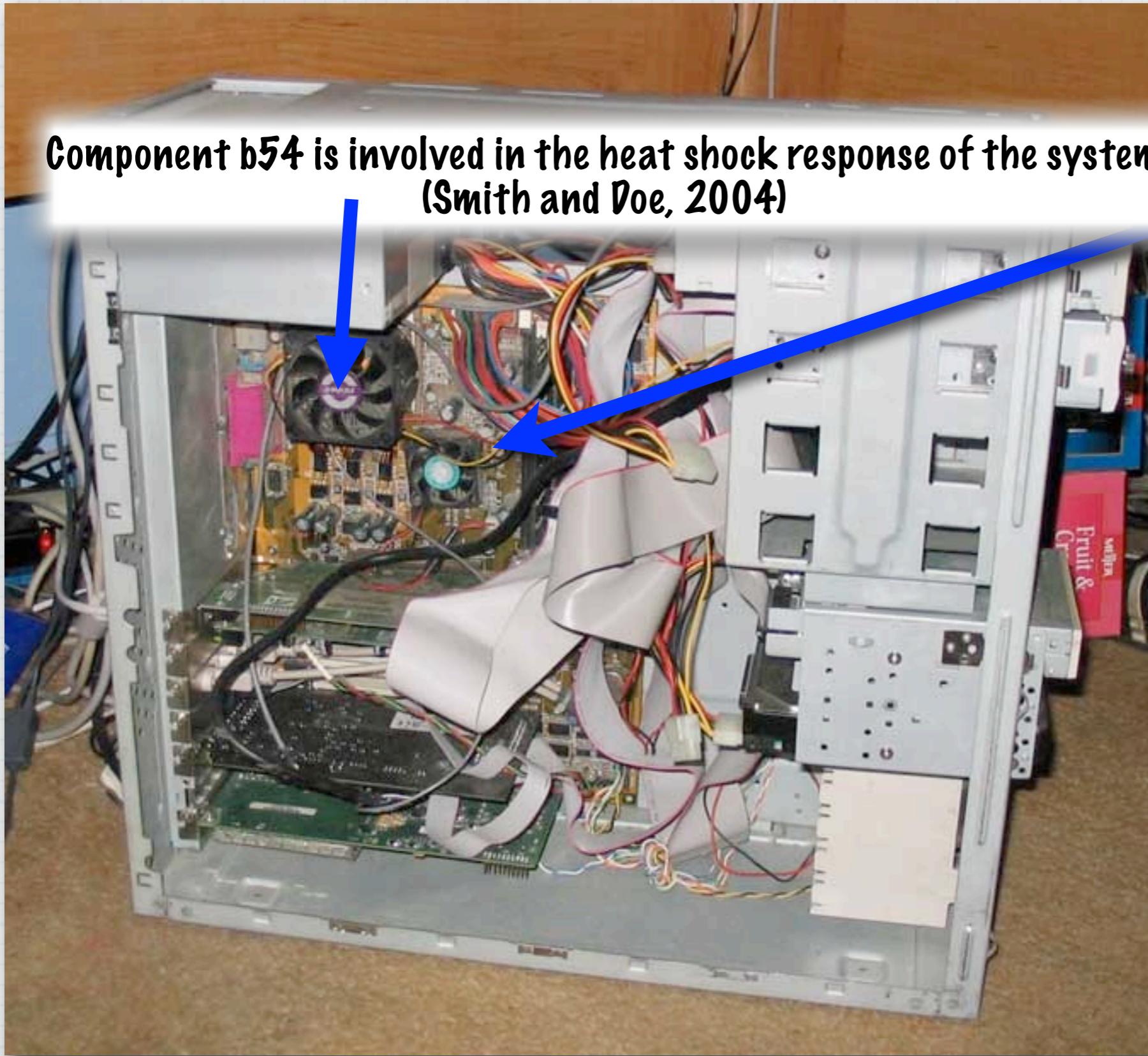
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Knock out:
Cut wire 'w'

How to build a network?

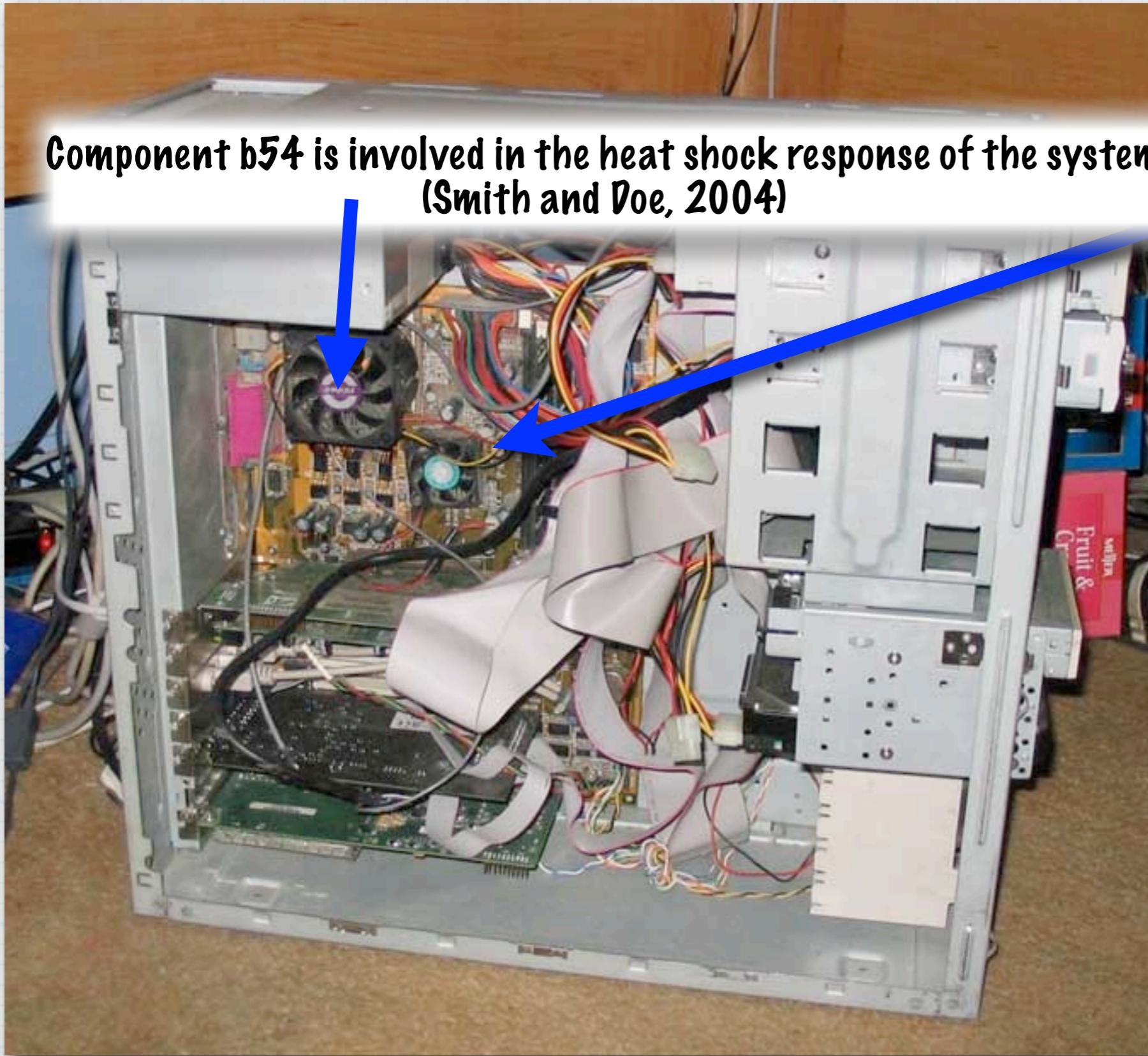


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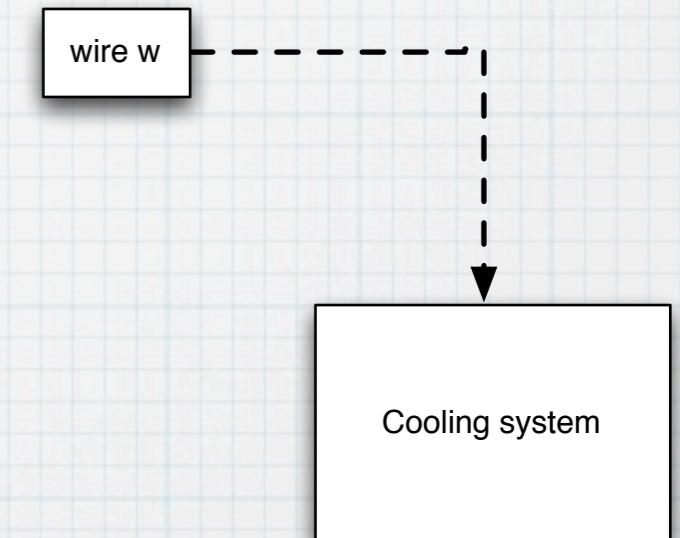
Observation:
computer's heat goes up!

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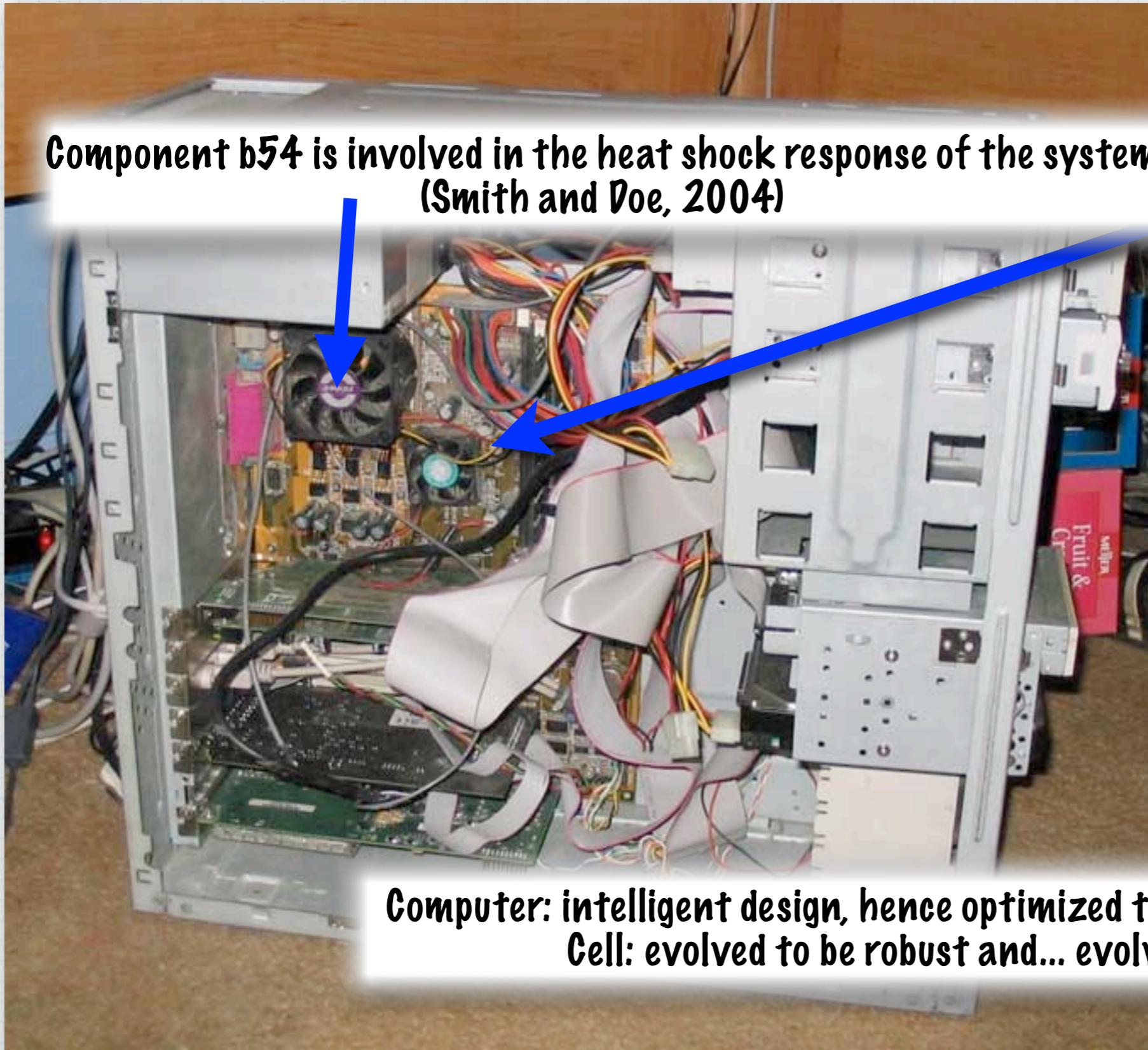


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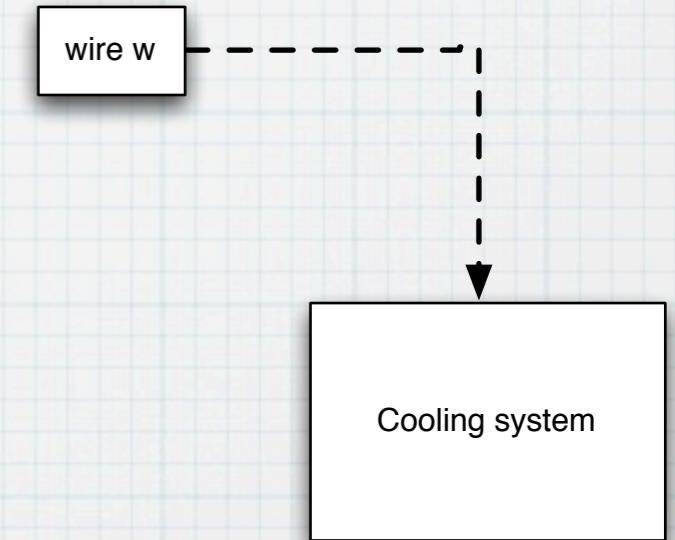


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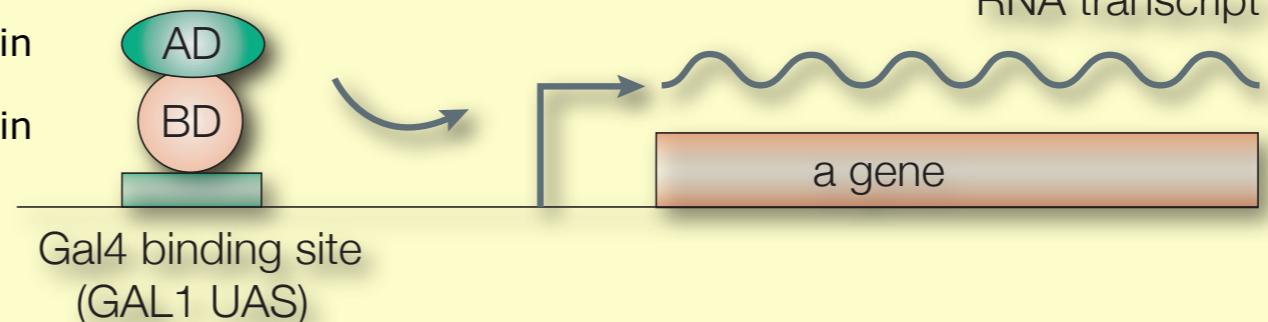
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obtaining protein-protein interaction data on a global scale

Gal4 transcriptional activation domain

Gal4 DNA-binding domain



biological process

1.

fuse protein X to the Gal4 DNA-binding domain



"BAIT"

fuse protein Y to the Gal4 transcriptional activation domain

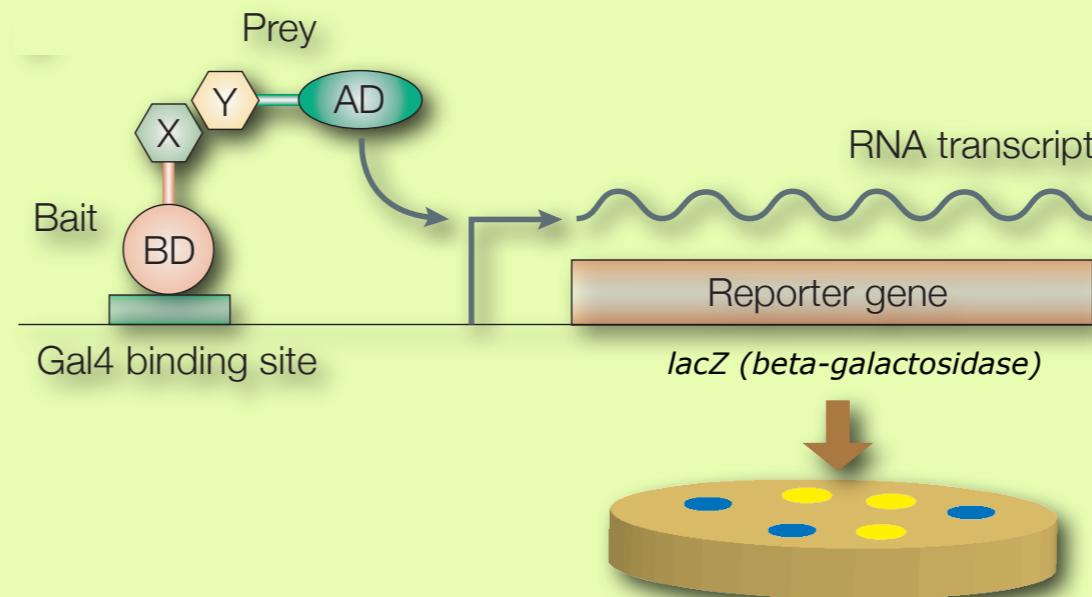


"PREY"

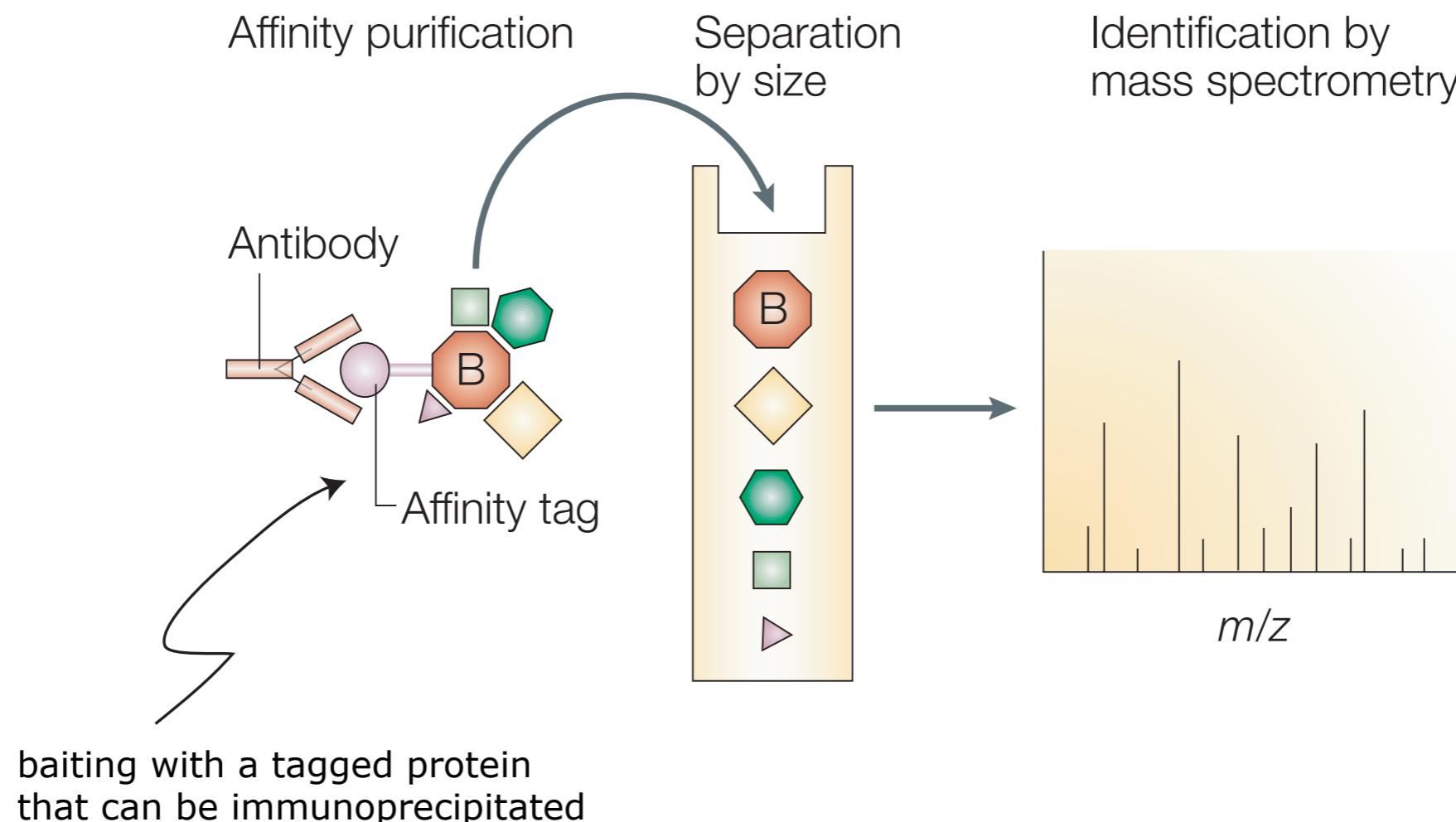
if X and Y bind, a reporter is expressed

2.

yeast two-hybrid assay



affinity purification: identifying protein complexes



Affinity purification yields the composition of a complex, but not the contact map.

yeast two-hybrid problems

- PCR introduces mutations that may abolish interaction
- fusion constructs may affect proper folding needed for interaction
- interaction may require activation of either bait or prey protein or both
- stochastic gene expression may generate false positives
- differences in experimental procedure (reporters, selection strategies)

90% of known interactions not found...

Of newly discovered interactions, 50% are estimated to be likely biologically relevant...

affinity purification problems

- adding a tag might interfere with complex formation (turned out to be even lethal at times)
- difficult to detect transient interactions, small proteins
- wrong conditions
- nonspecific binding
- error rates of 30% in repeated purification experiments

little overlap with Y2H...

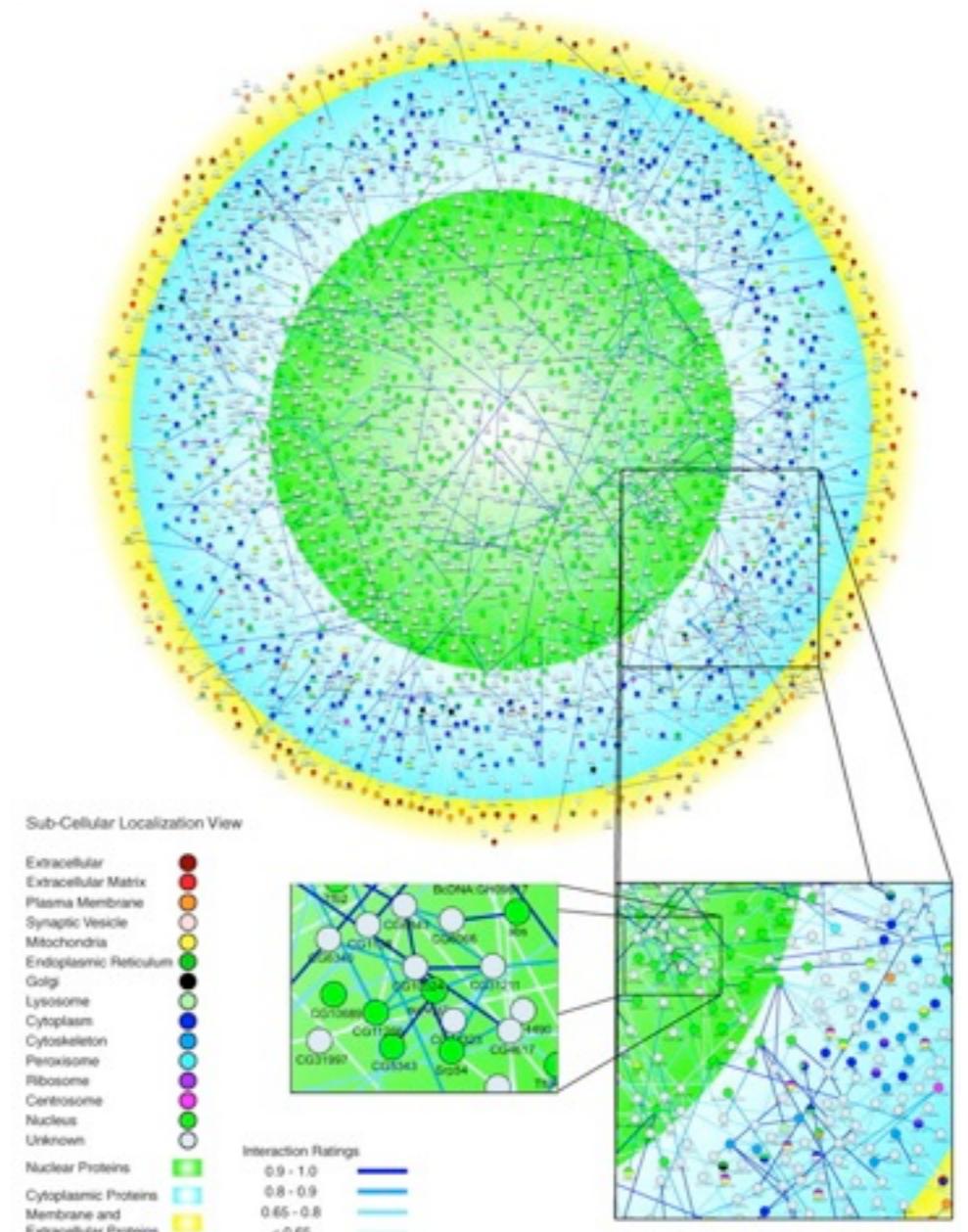
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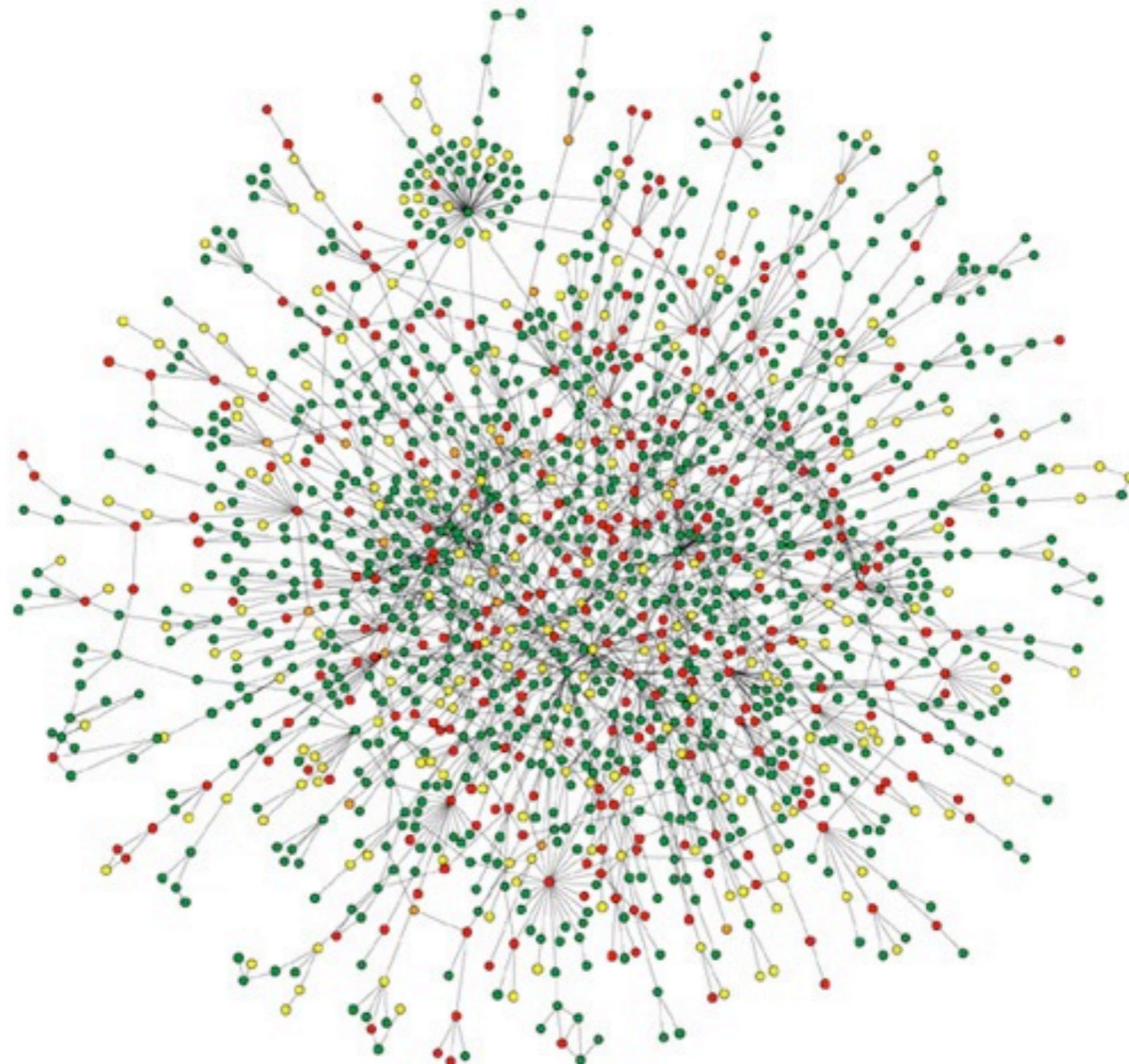
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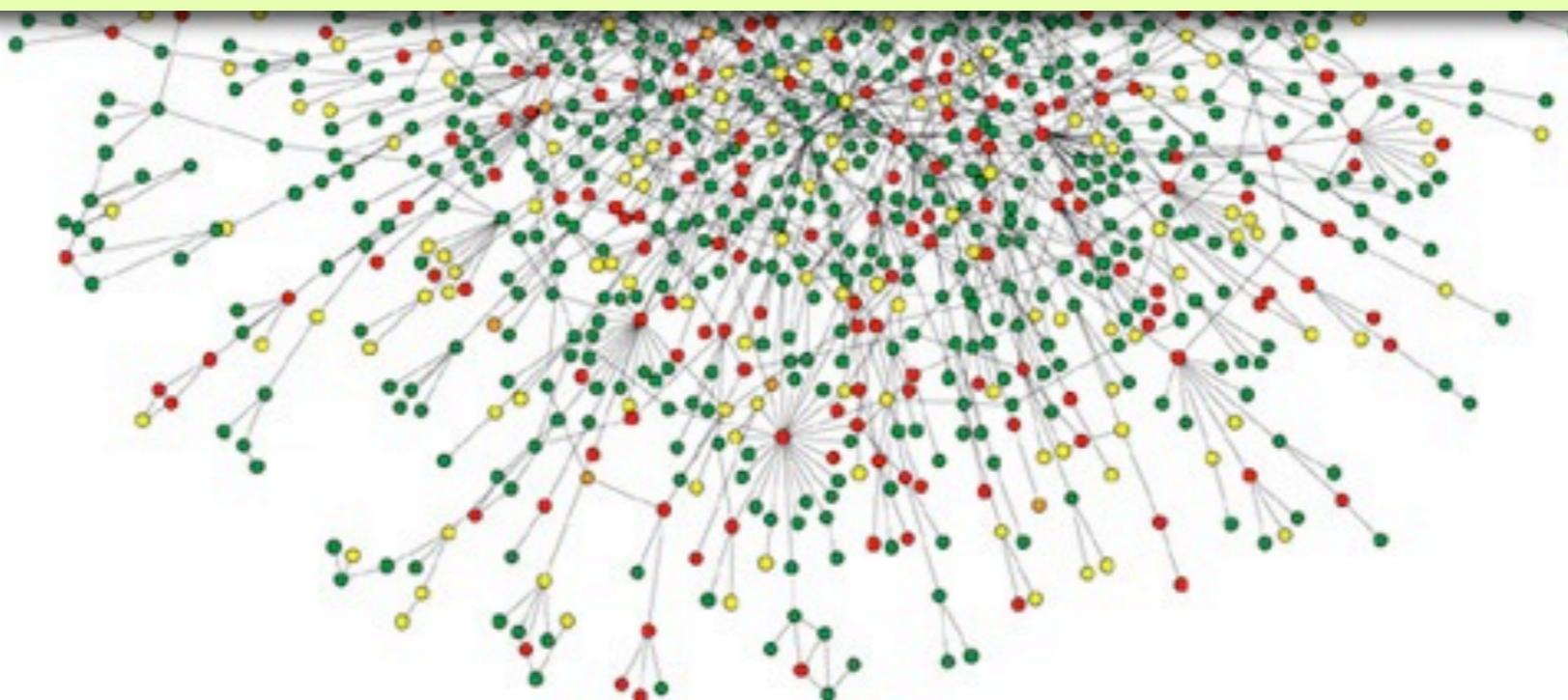
"What does a network look like, when you actually can't look at it?"



"What does a network look like, when you actually can't look at it?"



Modules are not in the static picture...

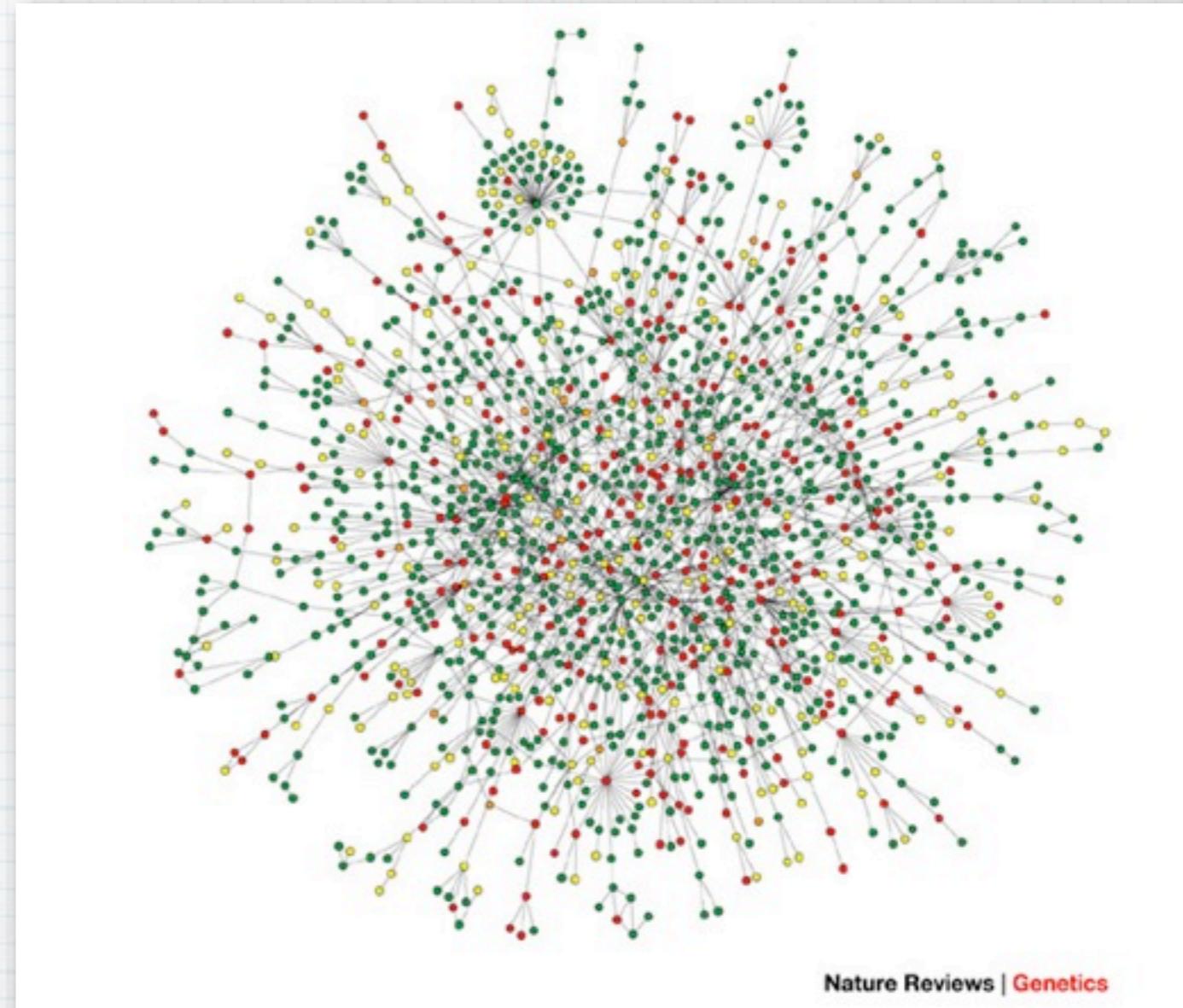


Dynamic network!

If complexes are highways that signals take on the way down to the nucleus....

Which complexes are effectively formed?

Which pathways are triggered on this dynamic network?



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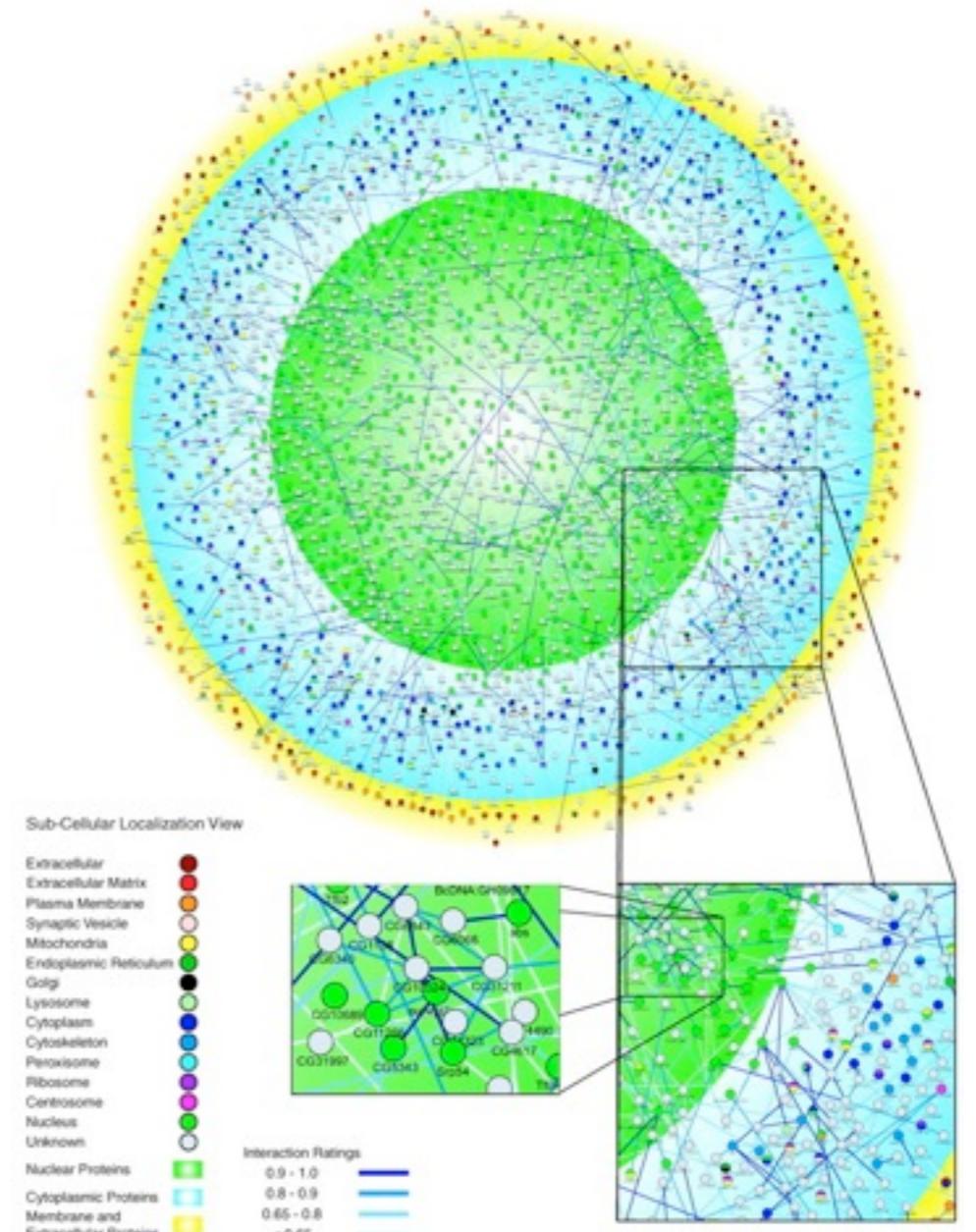
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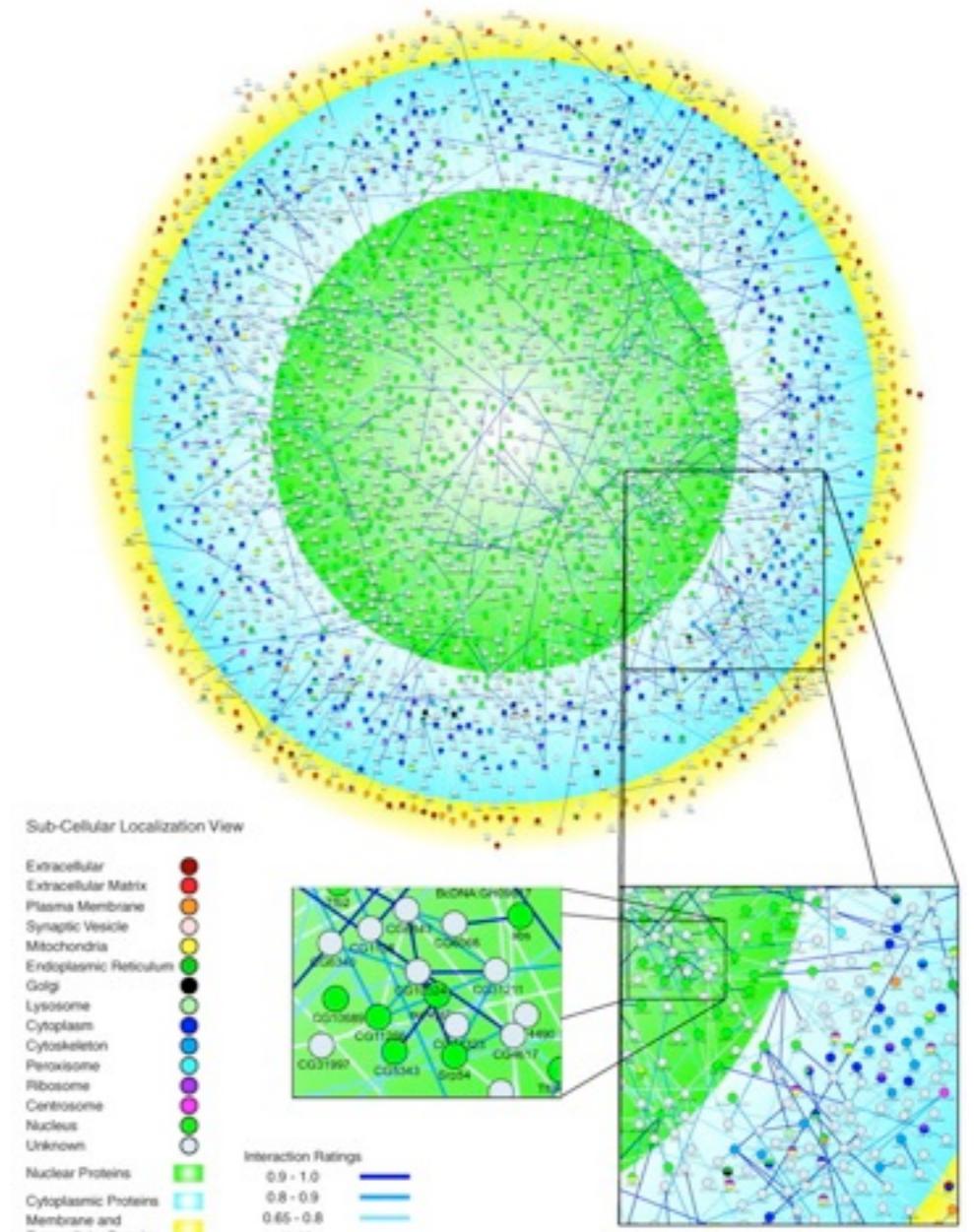
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modeling with Alice

Alice: Bob, what system do you want me to model?

Bob: A kinase K binds a substrate S and phosphorylates it at two sites a and b...

Alice: Bob, be more specific. Is the site that gets phosphorylated also the one to which the kinase binds? Is the mechanism processive or distributive? Can the kinase unbind? Can more than one kinase be bound to the same substrate?

Bob: ...Alice, be more patient. The kinase can only bind an unphosphorylated site. It binds the site that it phosphorylates. Only one kinase can be bound at any time. The kinase can dissociate at any time.

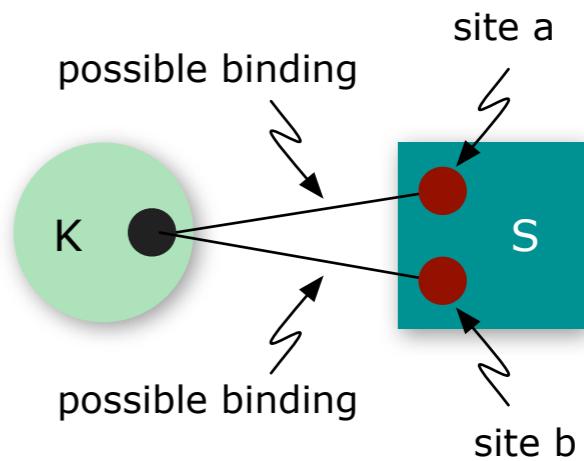
(Alice paces up and down scribbling on a piece of paper.)

Alice: Your assumptions produce 13 different molecular species:

- (i) substrate in all possible phosphorylation states: 4
- (ii) kinase bound at site a of S in all possible phosphorylation states: 4
- (ii) kinase bound at site b of S in all possible phosphorylation states: 4
- (iii) free kinase: 1

Bob: You wizard!

Alice: I will now set up 13 differential rate equations, one for each possible molecular species. Like in a ledger, each equation gathers all production and loss terms pertinent to a species according to your reactions. Here they are....



modeling with Alice

Alice:

$$\frac{d}{dt}x_1 = x_5 + x_9 + x_4 + x_3 + x_7 + x_8 + x_2 + x_6 - x_1x_{13} - x_1x_{13} - x_1x_{12} - x_1x_{11}$$

$$\frac{d}{dt}x_2 = x_3 - x_2$$

$$\frac{d}{dt}x_3 = x_1x_{11} - x_3 - x_3$$

$$\frac{d}{dt}x_4 = x_5 - x_4$$

$$\frac{d}{dt}x_5 = x_1x_{13} - x_5 - x_5$$

$$\frac{d}{dt}x_6 = x_7 - x_6$$

$$\frac{d}{dt}x_7 = x_1x_{12} - x_7 - x_7$$

$$\frac{d}{dt}x_8 = x_9 - x_8$$

$$\frac{d}{dt}x_9 = x_1x_{13} - x_9 - x_9$$

$$\frac{d}{dt}x_{10} = x_2 + x_6$$

$$\frac{d}{dt}x_{11} = x_3 + x_8 - x_1x_{11}$$

$$\frac{d}{dt}x_{12} = x_4 + x_7 - x_1x_{12}$$

$$\frac{d}{dt}x_{13} = x_5 + x_9 - x_1x_{13} - x_1x_{13}$$

modeling with Alice

Alice:

$$\frac{d}{dt}x_1 = x_5 + x_9 + x_4 + x_3 + x_7 + x_8 + x_2 + x_6 - x_1x_{13} - x_1x_{13} - x_1x_{12} - x_1x_{11}$$

$$\frac{d}{dt}x_2 = x_3 - x_2$$

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$$\frac{d}{dt}x_7 = x_1x_{12} - x_7 - x_7$$

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$$\frac{d}{dt}x_{13} = x_5 + x_9 - x_1x_{13} - x_1x_{13}$$

Bob: Hm.

Alice: Hm - what?

Bob: Well, I guess each term corresponds to a reaction in my system. But if I give these equations to my boss, she won't have a clue what they model.

Alice: Well, you have to give your boss your diagram as well.

Bob: Hm.

Alice: Well, a key might help too.

$$x_1 = [K]$$

$$x_2 = [K_a S_{ab}]$$

$$x_3 = [K_a S_b]$$

$$x_4 = [K_a S_a]$$

$$x_5 = [K_a S]$$

$$x_6 = [K_b S_{ab}]$$

$$x_7 = [K_b S_a]$$

$$x_8 = [K_b S_b]$$

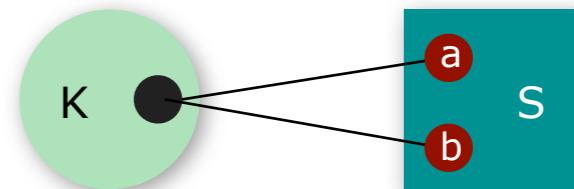
$$x_9 = [K_b S]$$

$$x_{10} = [S_{ab}]$$

$$x_{11} = [S_b]$$

$$x_{12} = [S_a]$$

$$x_{13} = [S]$$



modeling with Alice

(Bob comes running down the hallway.)

Bob: Aaaliice!

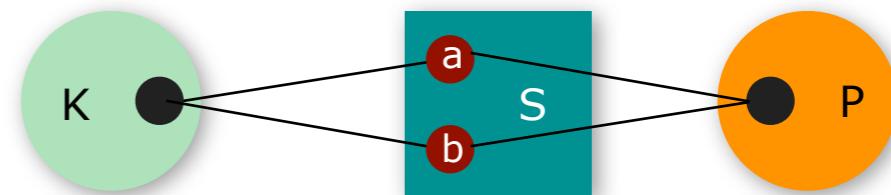
Alice: What?

Bob: My boss said: Bob, that's great.

Alice: Hey, you owe me!

Bob: My boss also said: Bob, you forgot the phosphatase!

Alice: Sh-t.



modeling with Alice



$$\frac{d}{dt}[K] = [K_a S] + [K_b S] + [K_a S_a] + [K_a S_b] + [K_b S_a] + [K_b S_b] + [K_a S_{ab}] + [K_b S_{ab}] - [K][S] - [K][S] - [K][S_a] - [K][S_b]$$

$$\frac{d}{dt}[K_a S_{ab}] = [K_a S_b] - [K_a S_{ab}]$$

$$\frac{d}{dt}[K_a S_b] = [K][S_b] - [K_a S_b] - [K_a S_b]$$

$$\frac{d}{dt}[K_a S_a] = [K_a S] - [K_a S_a]$$

$$\frac{d}{dt}[K_a S] = [K][S] - [K_a S] - [K_a S]$$

$$\frac{d}{dt}[K_b S_{ab}] = [K_b S_a] - [K_b S_{ab}]$$

$$\frac{d}{dt}[K_b S_a] = [K][S_a] - [K_b S_a] - [K_b S_a]$$

$$\frac{d}{dt}[K_b S_b] = [K_b S] - [K_b S_b]$$

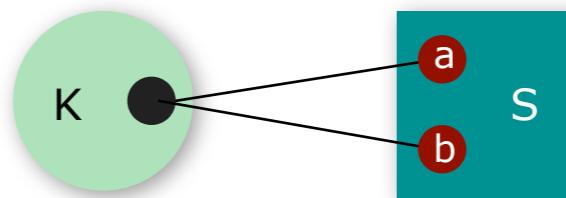
$$\frac{d}{dt}[K_b S] = [K][S] - [K_b S] - [K_b S]$$

$$\frac{d}{dt}[S_{ab}] = [K_a S_{ab}] + [K_b S_{ab}]$$

$$\frac{d}{dt}[S_b] = [K_a S_b] + [K_b S_b] - [K][S_b]$$

$$\frac{d}{dt}[S_a] = [K_a S_a] + [K_b S_a] - [K][S_a]$$

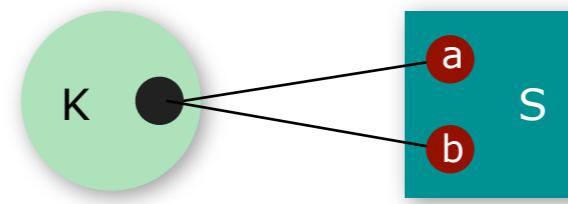
$$\frac{d}{dt}[S] = [K_a S] + [K_b S] - [K][S] - [K][S]$$



without a phosphatase

modeling with Alice

$$\frac{d}{dt}[K] = \text{●} + \text{●} - \text{●} - \text{●} - \text{●} - \text{●}$$
$$\frac{d}{dt}[K_a S_{ab}] = \text{●} - \text{●}$$
$$\frac{d}{dt}[K_a S_b] = \text{●} - \text{●} - \text{●}$$
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$$\frac{d}{dt}[K_a S] = \text{●} - \text{●} - \text{●}$$
$$\frac{d}{dt}[K_b S_{ab}] = \text{●} - \text{●}$$
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$$\frac{d}{dt}[K_b S_b] = \text{●} - \text{●}$$
$$\frac{d}{dt}[K_b S] = \text{●} - \text{●} - \text{●}$$
$$\frac{d}{dt}[S_{ab}] = \text{●} + \text{●}$$
$$\frac{d}{dt}[S_b] = \text{●} + \text{●} - \text{●}$$
$$\frac{d}{dt}[S_a] = \text{●} + \text{●} - \text{●}$$
$$\frac{d}{dt}[S] = \text{●} + \text{●} - \text{●} - \text{●}$$



without a phosphatase

modeling with Alice

$$\frac{d}{dt}[K] = \bullet + \bullet + \bullet + \bullet + \bullet + \bullet + \bullet - \bullet - \bullet - \bullet + \bullet - \bullet - \bullet$$

$$\frac{d}{dt}[K_a S_{ab}] = \bullet - \bullet + \bullet + \bullet$$

$$\frac{d}{dt}[K_a S_b] = \bullet - \bullet - \bullet + \bullet + \bullet$$

$$\frac{d}{dt}[K_a S_a] = \bullet - \bullet + \bullet$$

$$\frac{d}{dt}[K_a S] = \bullet - \bullet - \bullet + \bullet$$

$$\frac{d}{dt}[K_b S_{ab}] = \bullet - \bullet + \bullet + \bullet$$

$$\frac{d}{dt}[K_b S_a] = \bullet - \bullet - \bullet + \bullet + \bullet$$

$$\frac{d}{dt}[K_b S_b] = \bullet - \bullet + \bullet$$

$$\frac{d}{dt}[K_b S] = \bullet - \bullet - \bullet + \bullet$$

$$\frac{d}{dt}[S_{ab}] = \bullet + \bullet + \bullet + \bullet$$

$$\frac{d}{dt}[S_b] = \bullet + \bullet + \bullet + \bullet - \bullet - \bullet$$

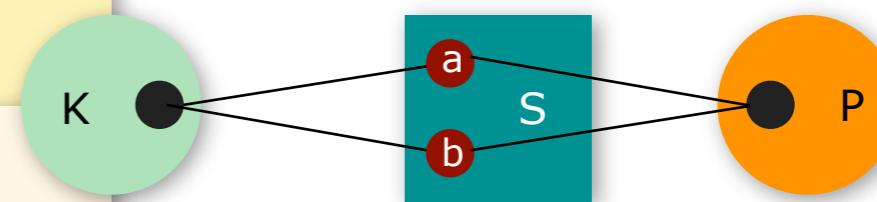
$$\frac{d}{dt}[S_a] = \bullet + \bullet + \bullet + \bullet - \bullet - \bullet$$

$$\frac{d}{dt}[S] = \bullet + \bullet - \bullet - \bullet + \bullet + \bullet$$

13 old equations, but each now

13 old equations, but each now needs to be changed

+ 21 new equations



adding a phosphatase

What are the limitations of the dynamical systems (ODE) approach?

1

the formalism of differential equations does not represent **agents**, only their concentration

- ⇒ need to know in advance all molecular species that can occur
- ⇒ vulnerable to combinatorial explosions
- ⇒ cumbersome to build and modify large models

2

the formalism of differential equations entangles kinetics and **causation**

- ⇒ physical time is inadequate for describing distributed systems
- ⇒ hard to reason about “mechanisms of action”

3

the formalism of differential equations separates model and **knowledge**

- ⇒ “I forgot why I put this term in my model...”
- ⇒ models are not self-documenting and don’t organize knowledge effectively

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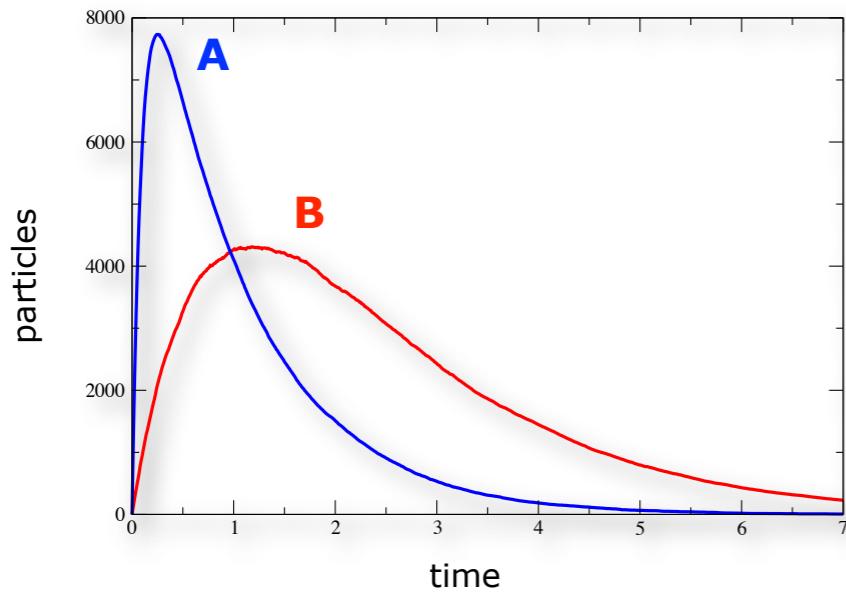
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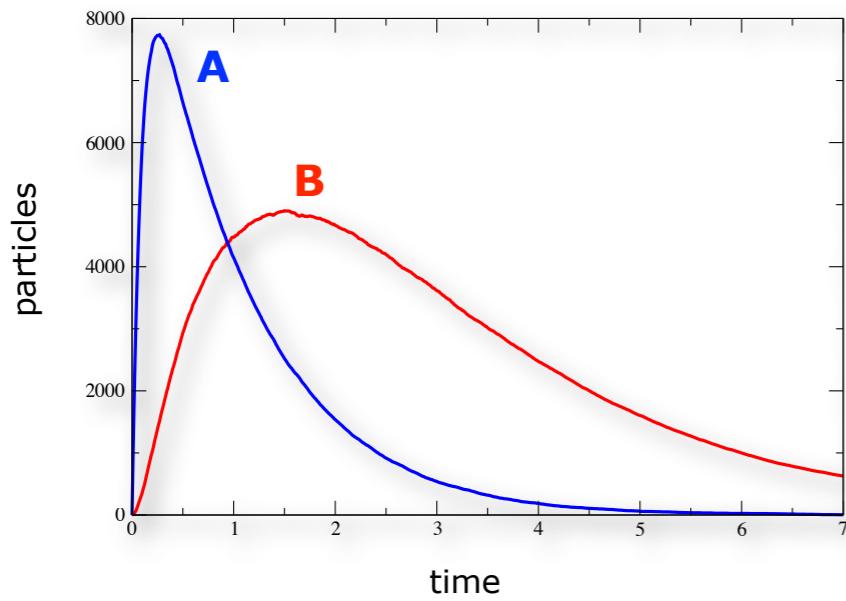
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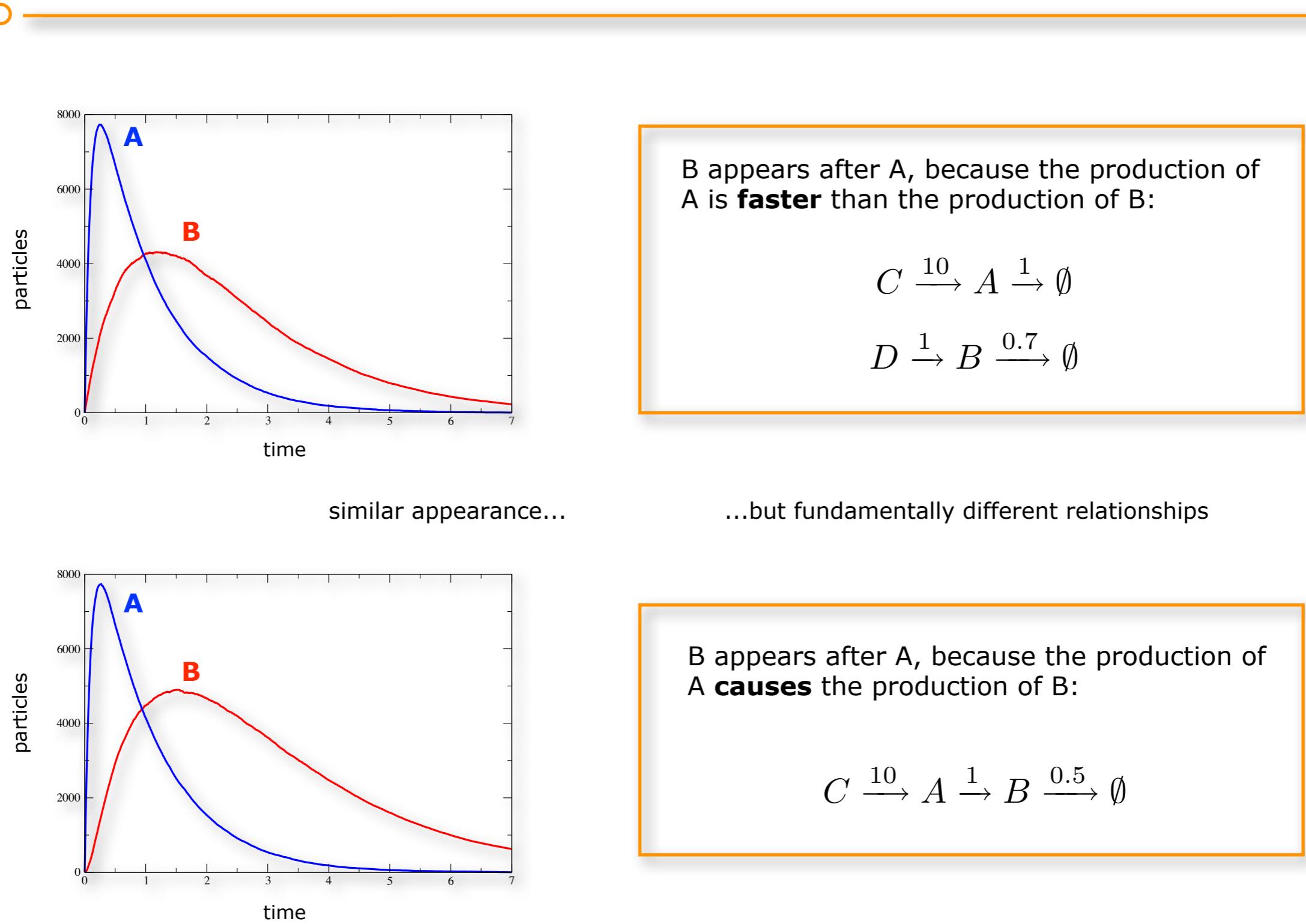
2 - the formalism of differential equations entangles kinetics and causation



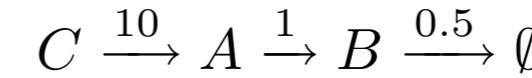
similar appearance...



2 - the formalism of differential equations entangles kinetics and causation



B appears after A, because the production of A **causes** the production of B:



The ODE formalism does not lend itself to causal analysis.

(In this example, we quickly inspect the reactions, but our brains cannot process 1000s of them.)

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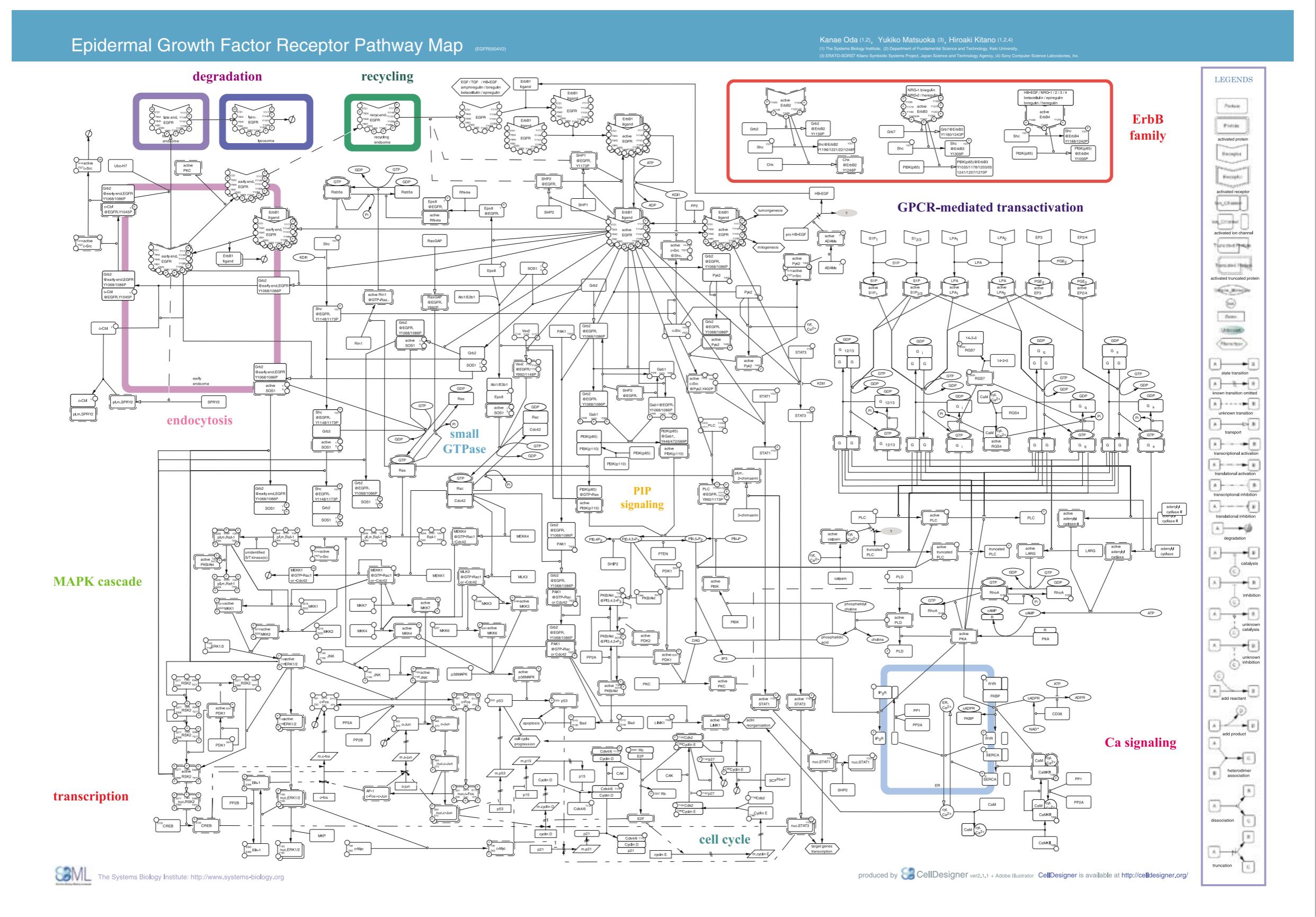
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Model as a review...



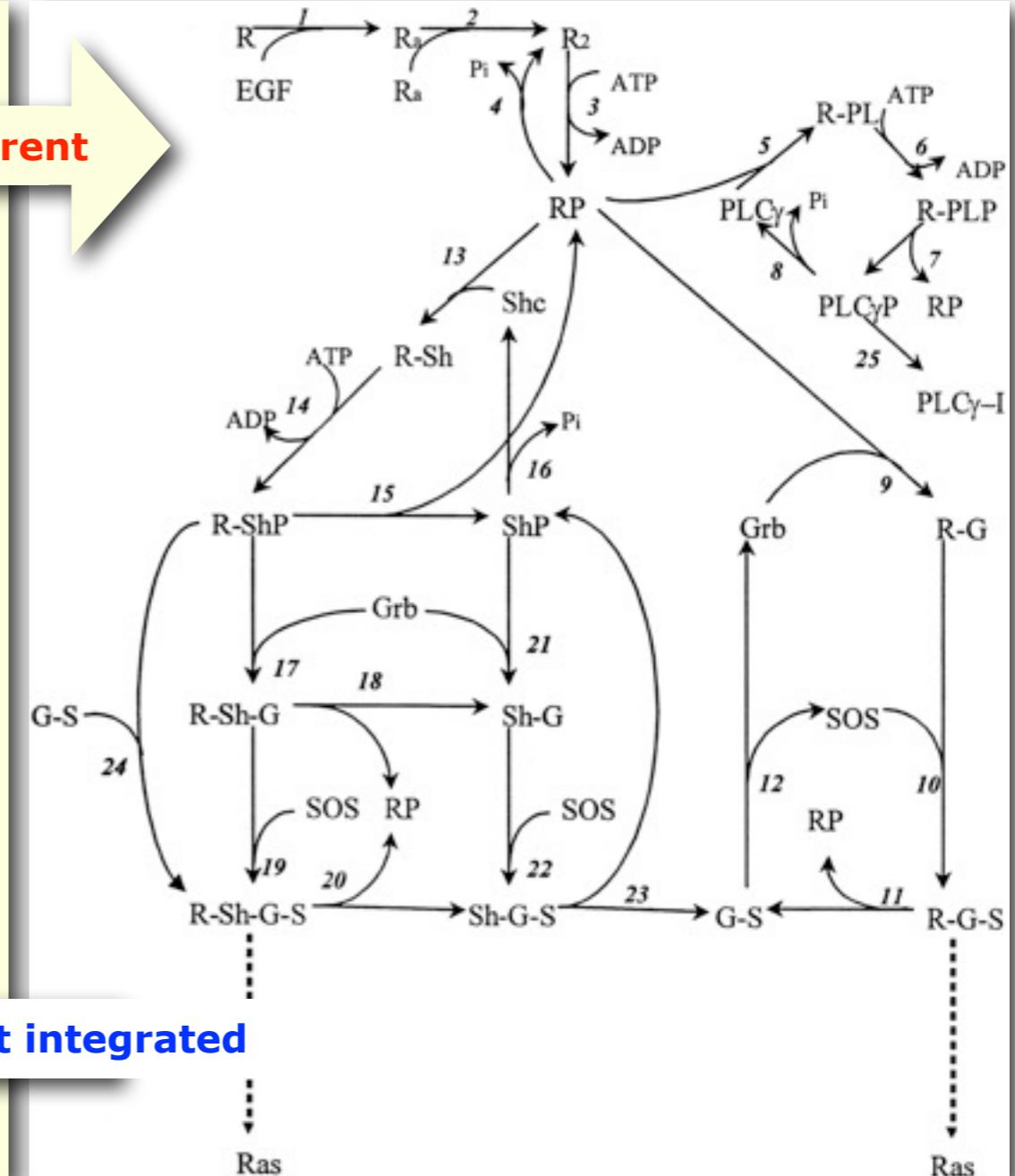
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ODE model

$$\begin{aligned}\frac{d}{dt}x_1 &= -k_1 \cdot x_2 \cdot x_1 + k_{-1} \cdot x_3 \\ \frac{d}{dt}x_2 &= -k_1 \cdot x_2 \cdot x_1 + k_{-1} \cdot x_3 \\ \frac{d}{dt}x_3 &= k_1 \cdot x_2 \cdot x_1 - k_{-1} \cdot x_3 - 2 \cdot (k_2 \cdot x_3 \cdot x_3 - k_{-2} \cdot x_4) \\ \frac{d}{dt}x_4 &= k_2 \cdot x_3 \cdot x_3 - k_{-2} \cdot x_4 + \frac{v_4 \cdot x_5}{p_4 + x_5} - (k_3 \cdot x_4 - k_{-3} \cdot x_5) \\ \frac{d}{dt}x_5 &= k_3 \cdot x_4 - k_{-3} \cdot x_5 + k_7 \cdot x_7 - k_{-7} \cdot x_5 \cdot x_{13} + k_{11} \cdot x_9 - \\ &\quad - k_{-11} \cdot x_5 \cdot x_9 + k_{15} \cdot x_{11} - k_{-15} \cdot x_5 \cdot x_{15} + k_{18} \cdot x_{12} - \\ &\quad - k_{-18} \cdot x_5 \cdot x_{16} + k_{20} \cdot x_{13} - k_{-20} \cdot x_{17} \cdot x_5 - \left(\frac{v_4 \cdot x_5}{p_4 + x_5} + \right. \\ &\quad \left. + k_9 \cdot x_5 \cdot x_{15} - k_{-9} \cdot x_8 + k_5 \cdot x_5 \cdot x_{18} - k_{-5} \cdot x_6 \right) \\ \frac{d}{dt}x_6 &= \dots \\ &\vdots \\ \frac{d}{dt}x_n &= \dots\end{aligned}$$

not transparent

empirical schema of interaction mechanisms



not integrated

large ODE models do not facilitate the tracking knowledge

knowledge evolves

Specification

We want a model to be:

- I. Arguably derived from biological facts
(transparency)

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Direct interaction of Cbl with pTyr 1045 of the EGF receptor (EGFR) is required to sort the EGFR to lysosomes for degradation

Lene Melsæther Grøvdal^a, Espen Stang^a, Alexander Sorkin^b, Inger Helene Madshus^{a,*}

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Abstract

Mutation of the binding site for Cbl (Tyr1045) in the EGF receptor (EGFR) results in impaired ubiquitination but does not affect EGFR internalization. However, the Y1045F mutation resulted in strongly decreased degradation of the EGFR, as well as efficient recycling of

Specification

We want a model to be:

- I. Arguably derived from biological facts
(transparency)

2. Modifiable (modularity)

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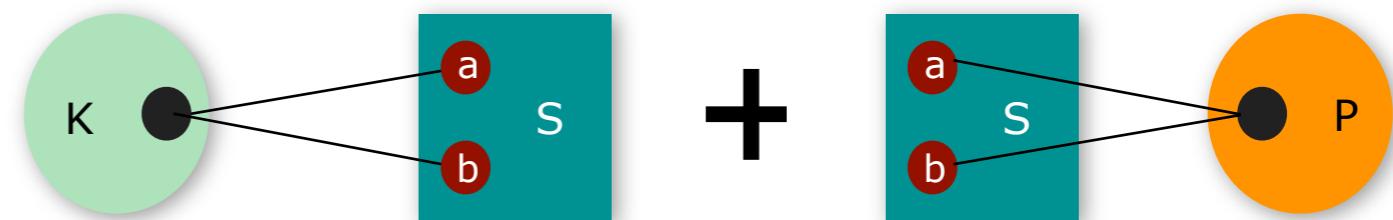
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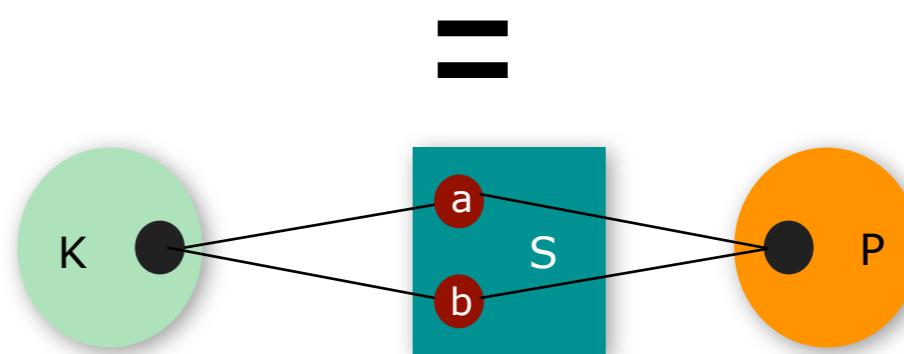
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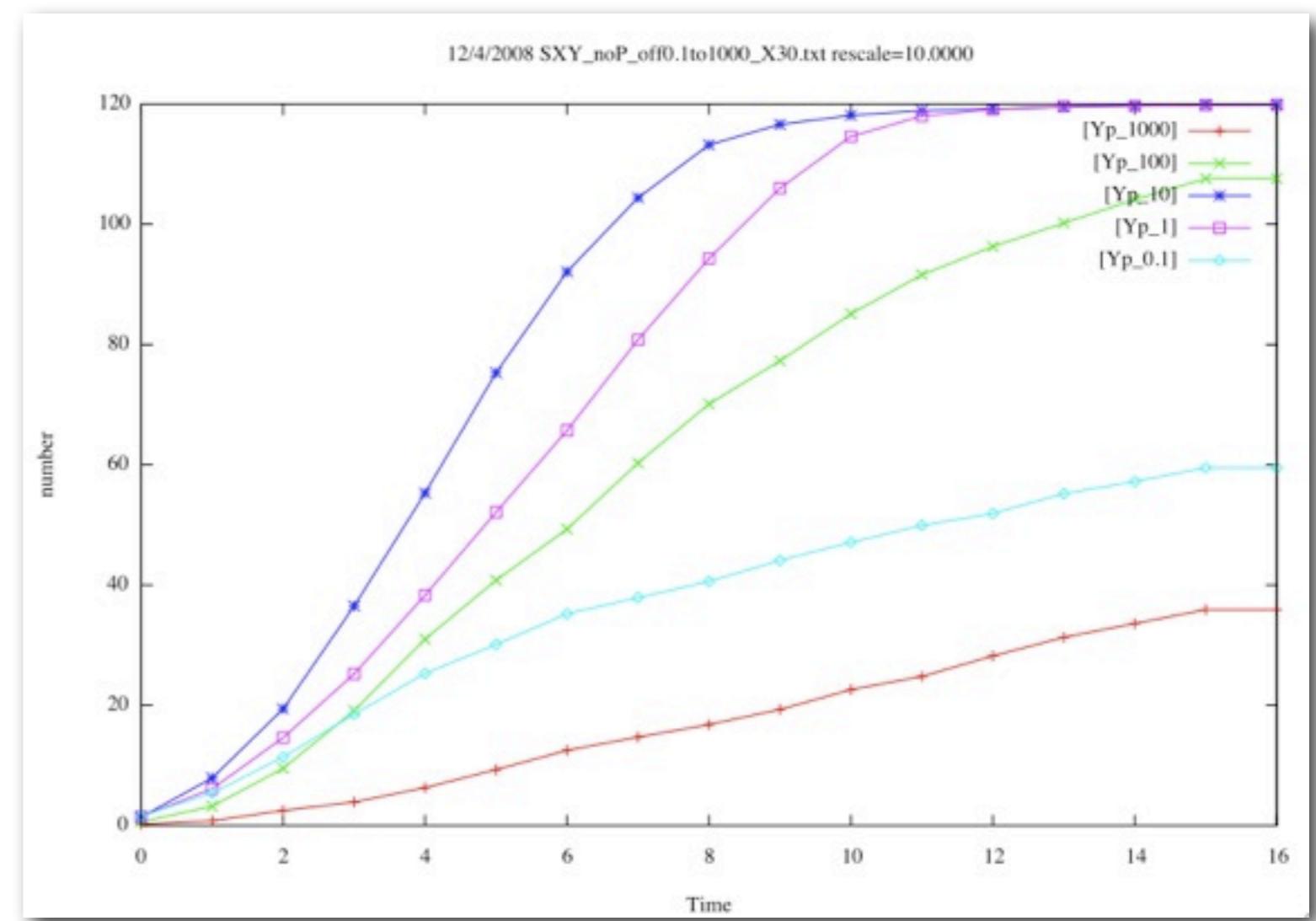
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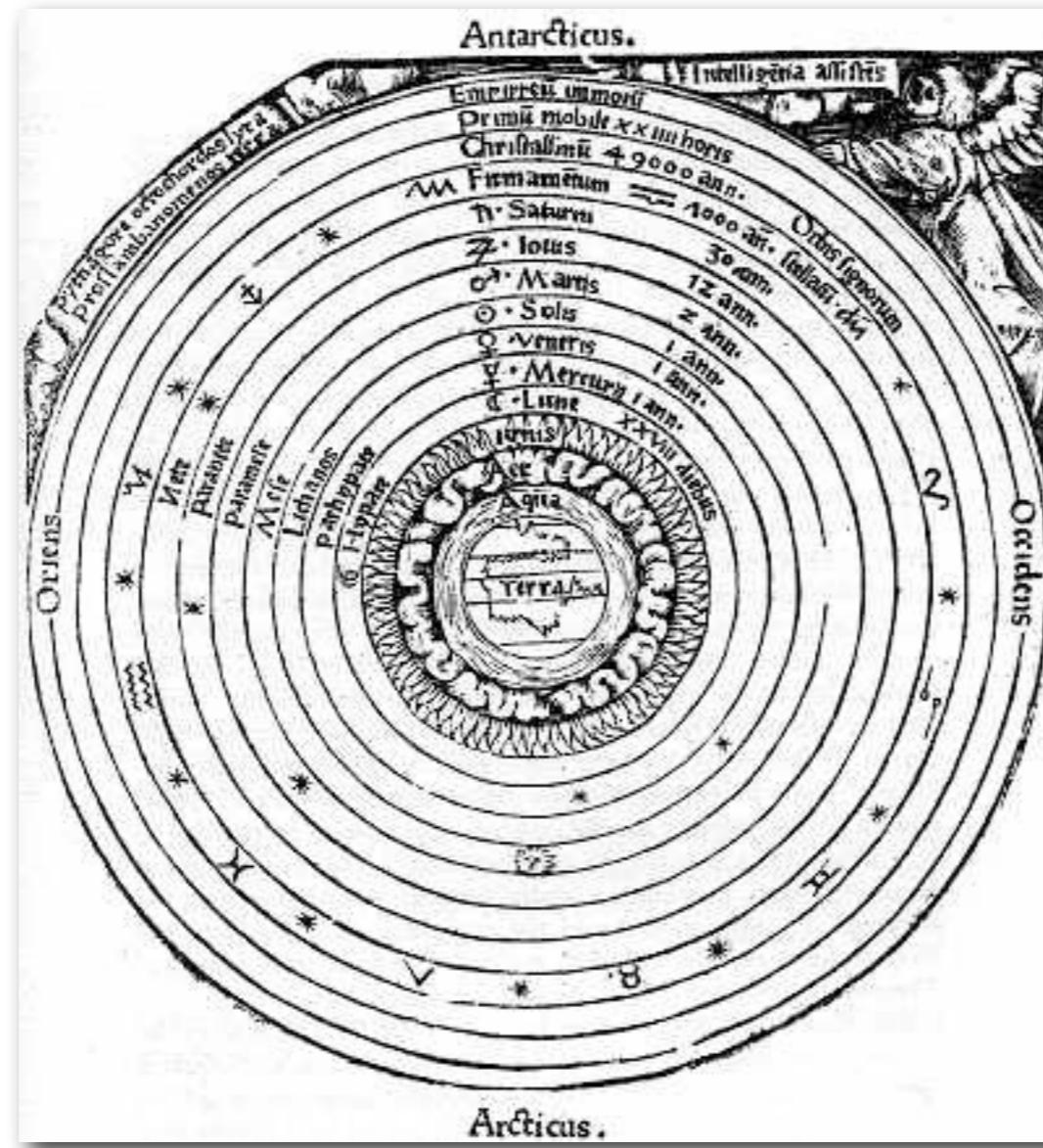
I. Arguably derived from biological facts
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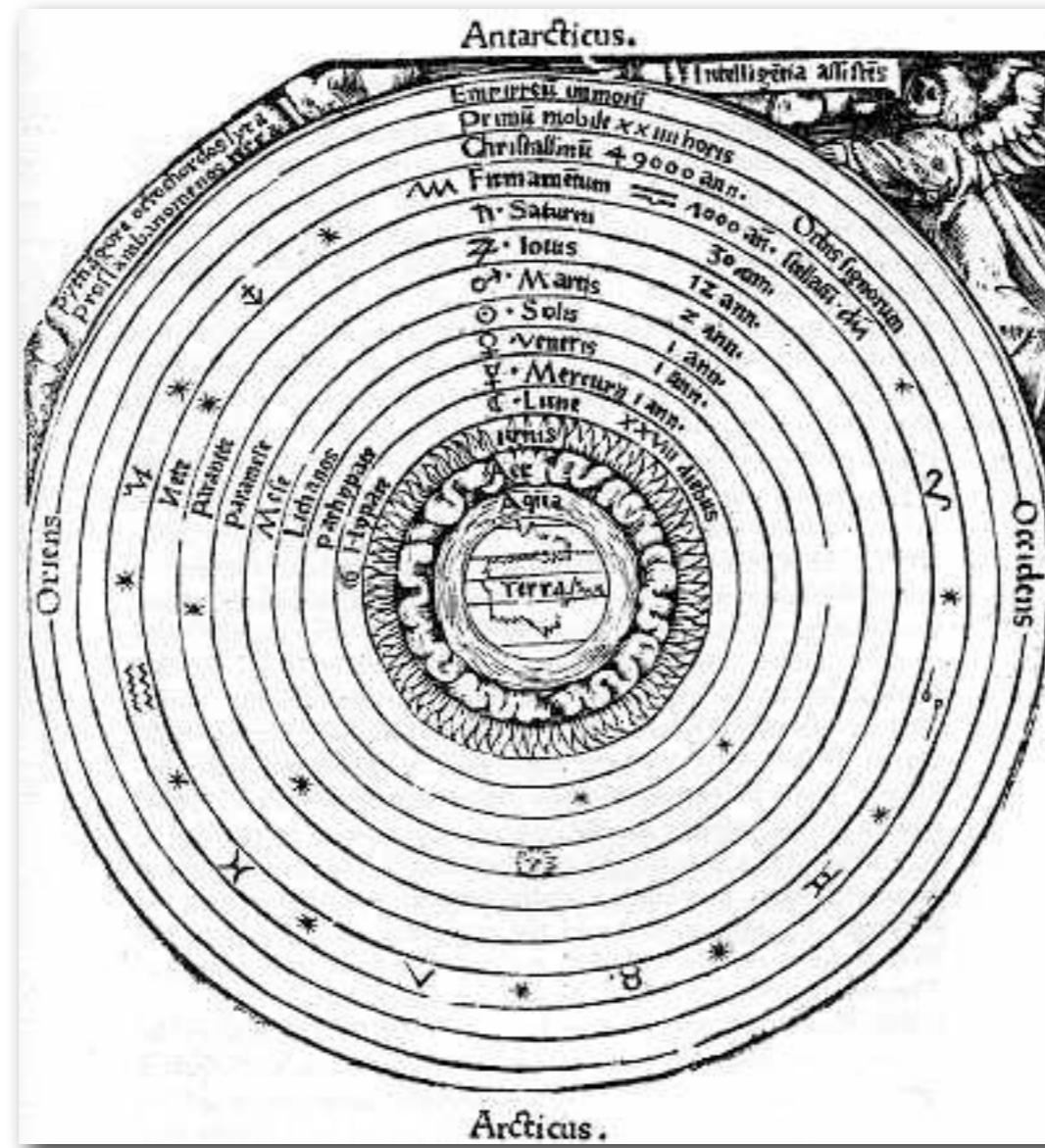
3. Executable (scalability!)



Incorrect but predictive power...

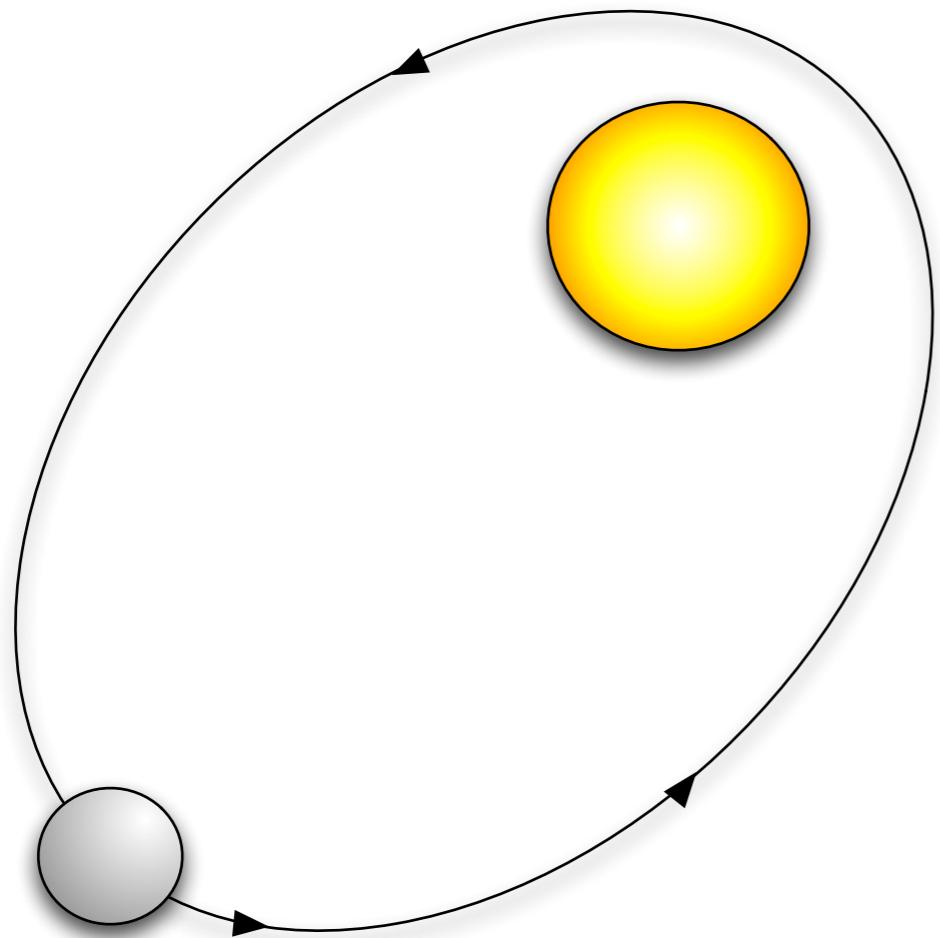


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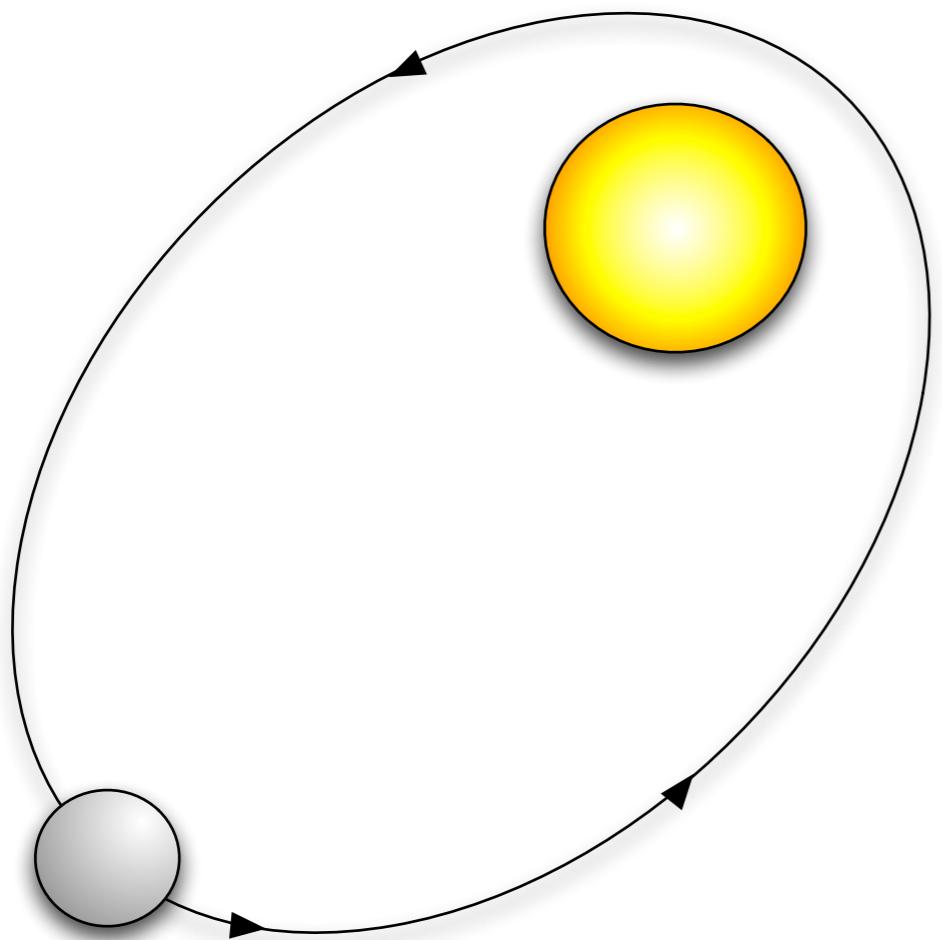
Ptolemaeus vs Copernicus

Not predictive but correct!

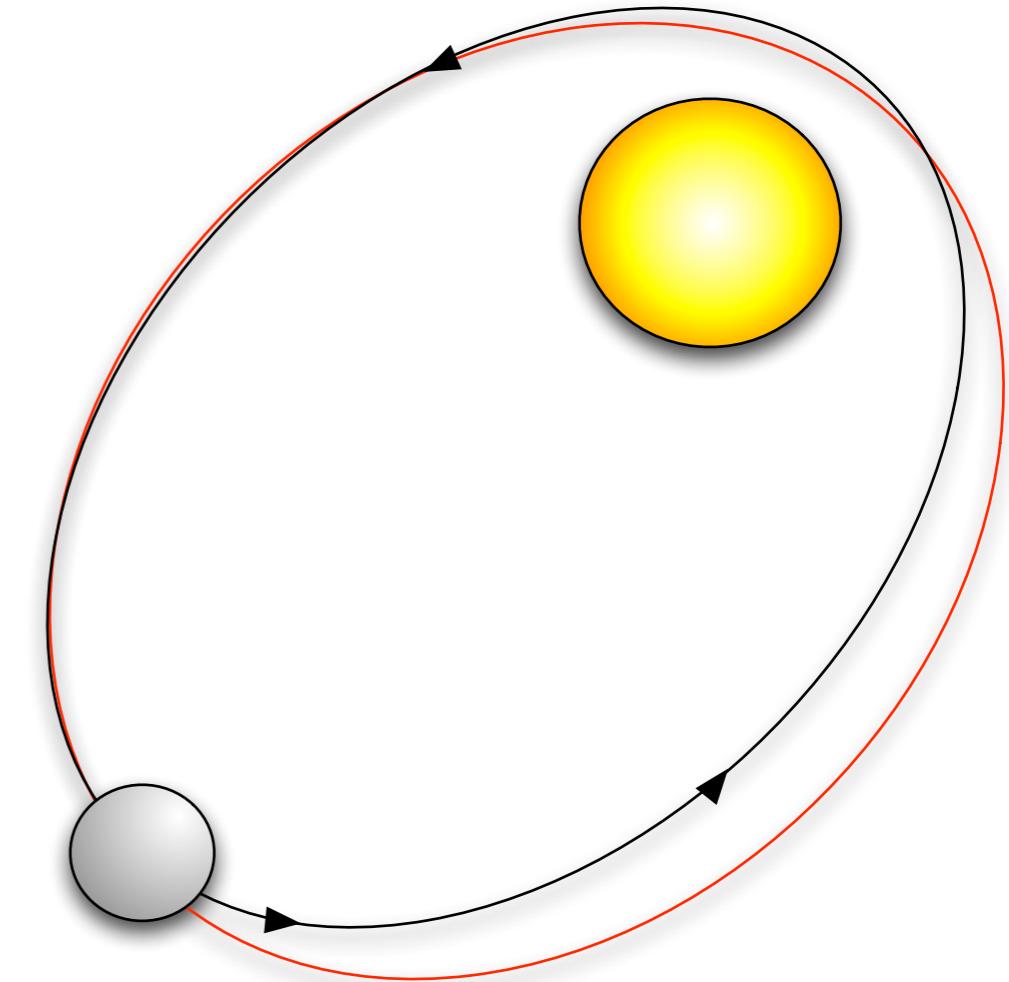


Prediction of a
program P

Not predictive but correct!



Prediction of a
program P



Observed trajectory

*T*rusting P allows one to hypothesize a missing planet!

...enter the land of rule-based modeling...

assume a spherical cow...

the world to a structural biologist



Law et al. *J.Biol.Chem.* **280**, 22356-64 (2005) PDB: 1WZ9, 1XU8

assume a spherical cow...

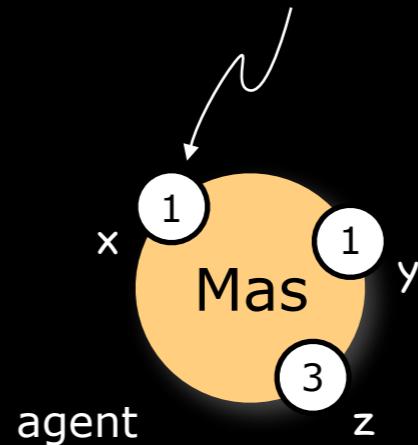


the world to a structural biologist

the world to us in this class...

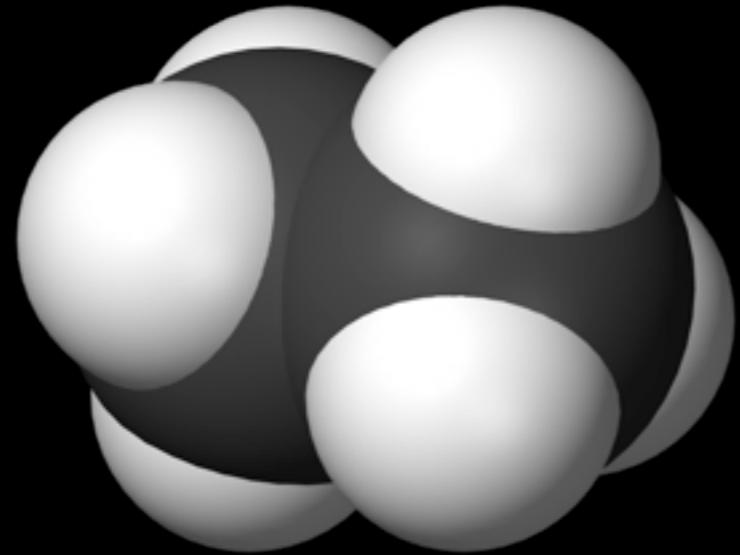


a *site with a state* represents
an interaction capability

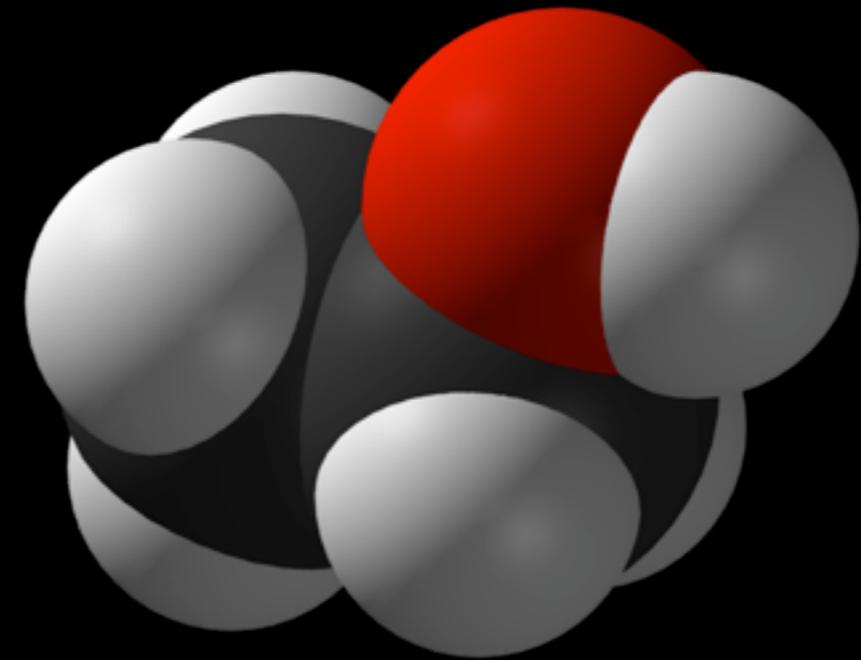


Law et al. *J.Biol.Chem.* **280**, 22356-64 (2005) PDB: IWZ9, IXU8

agent identity



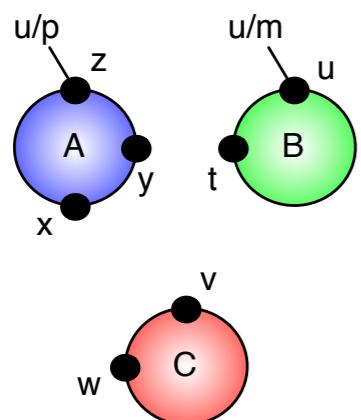
ethane



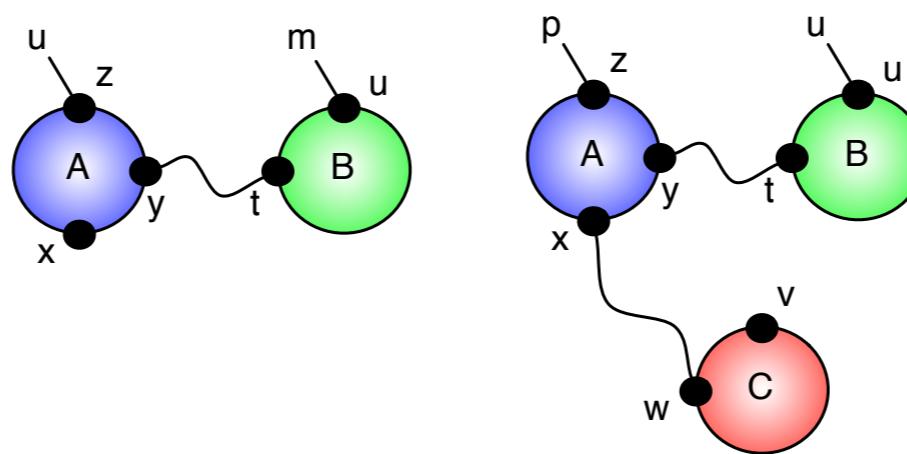
ethanol

Not “the same molecule in a different state”, but rather two different types of molecules!

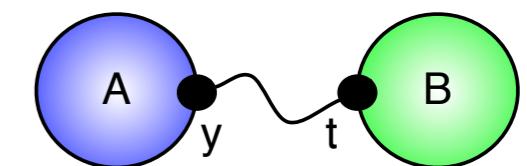
The cell as a graph



Proteins (nodes)



Species
(connected
components)

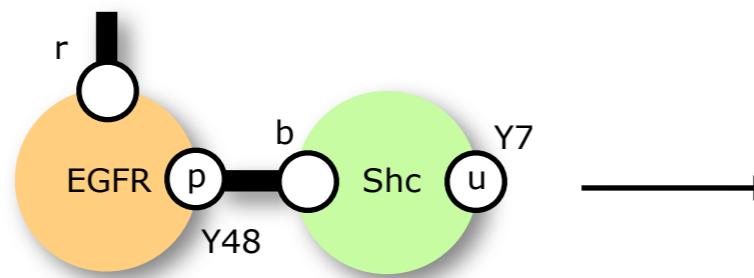


Expression
(pattern)

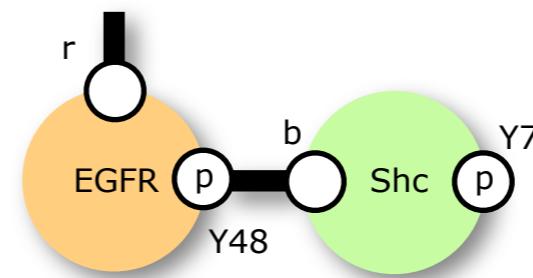
the language (kappa) : rules

a rule rewrites a pattern:

left pattern



right pattern

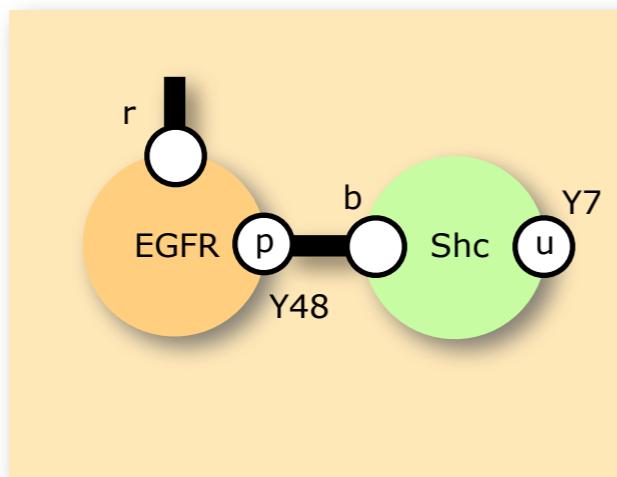


$$EGFR(r!-, Y48 \sim p!1), Shc(b!1, Y7 \sim u) \longrightarrow EGFR(r!-, Y48 \sim p!1), Shc(b!1, Y7 \sim p)$$

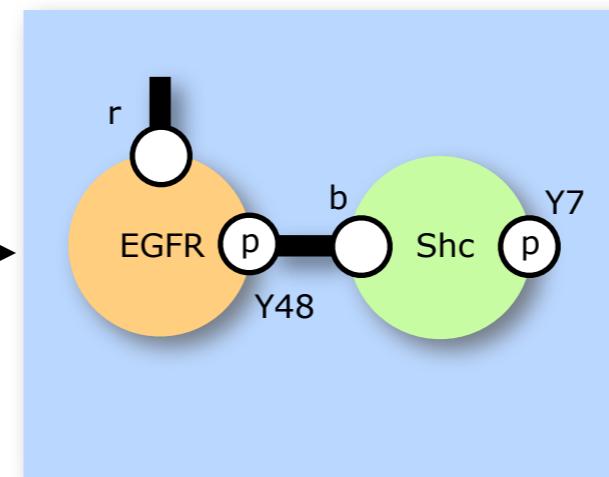
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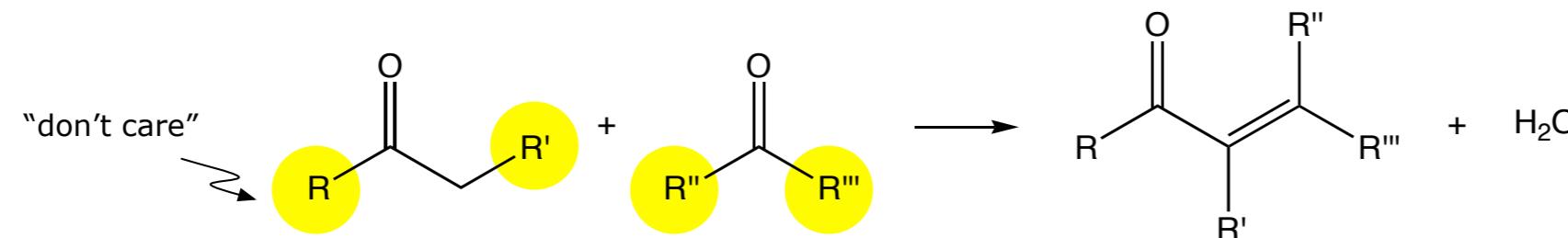
$$EGFR(r!-, Y48 \sim p!1), Shc(b!1, Y7 \sim u) \longrightarrow EGFR(r!-, Y48 \sim p!1), Shc(b!1, Y7 \sim p)$$

kappa is analogous to organic chemistry, but aimed at molecular biology



the rule (pattern) of an aldol condensation

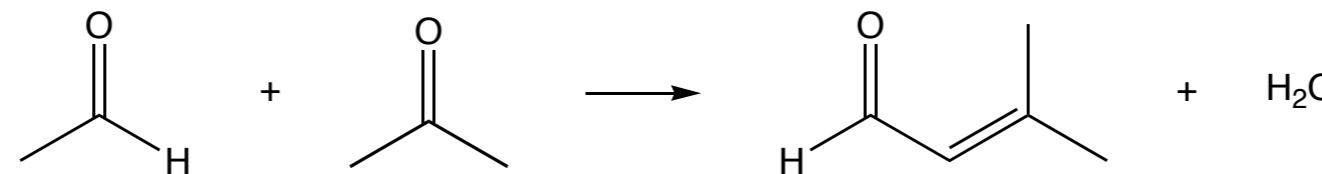
rule



instance

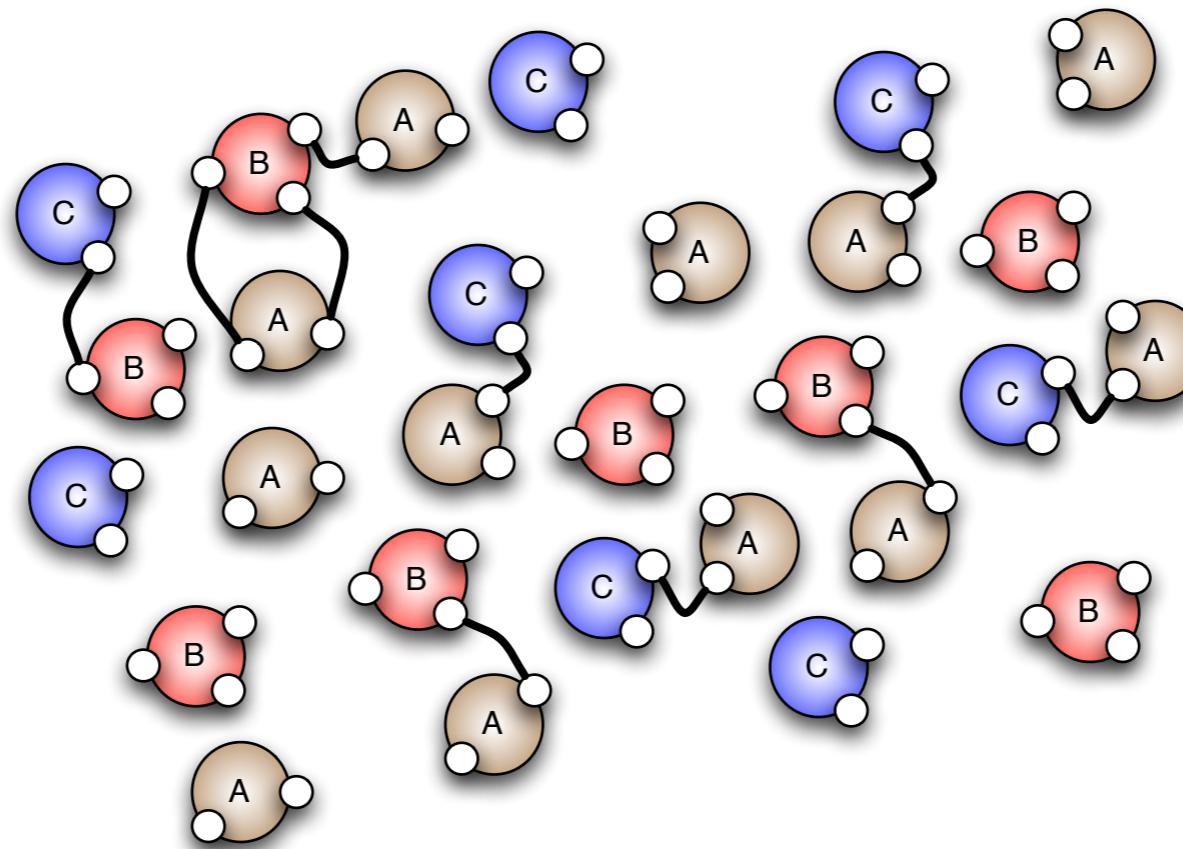
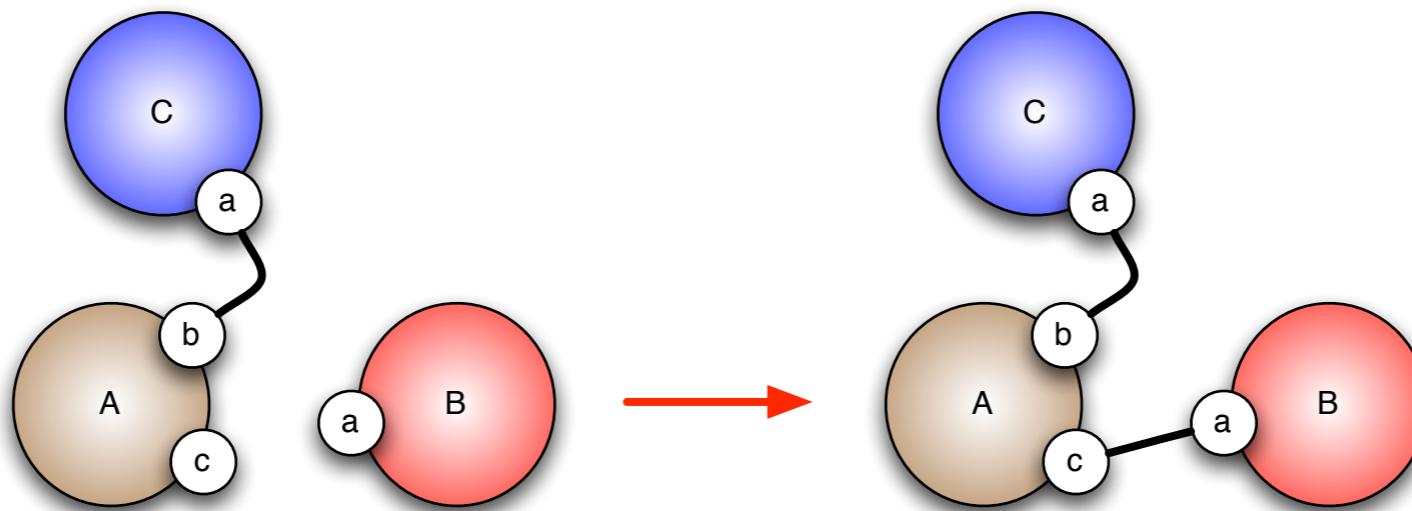
an instance of an aldol condensation (a "flat" or "fully contextualized" reaction)

R=H, R'=H, R''=CH₃,
R'''=CH₃



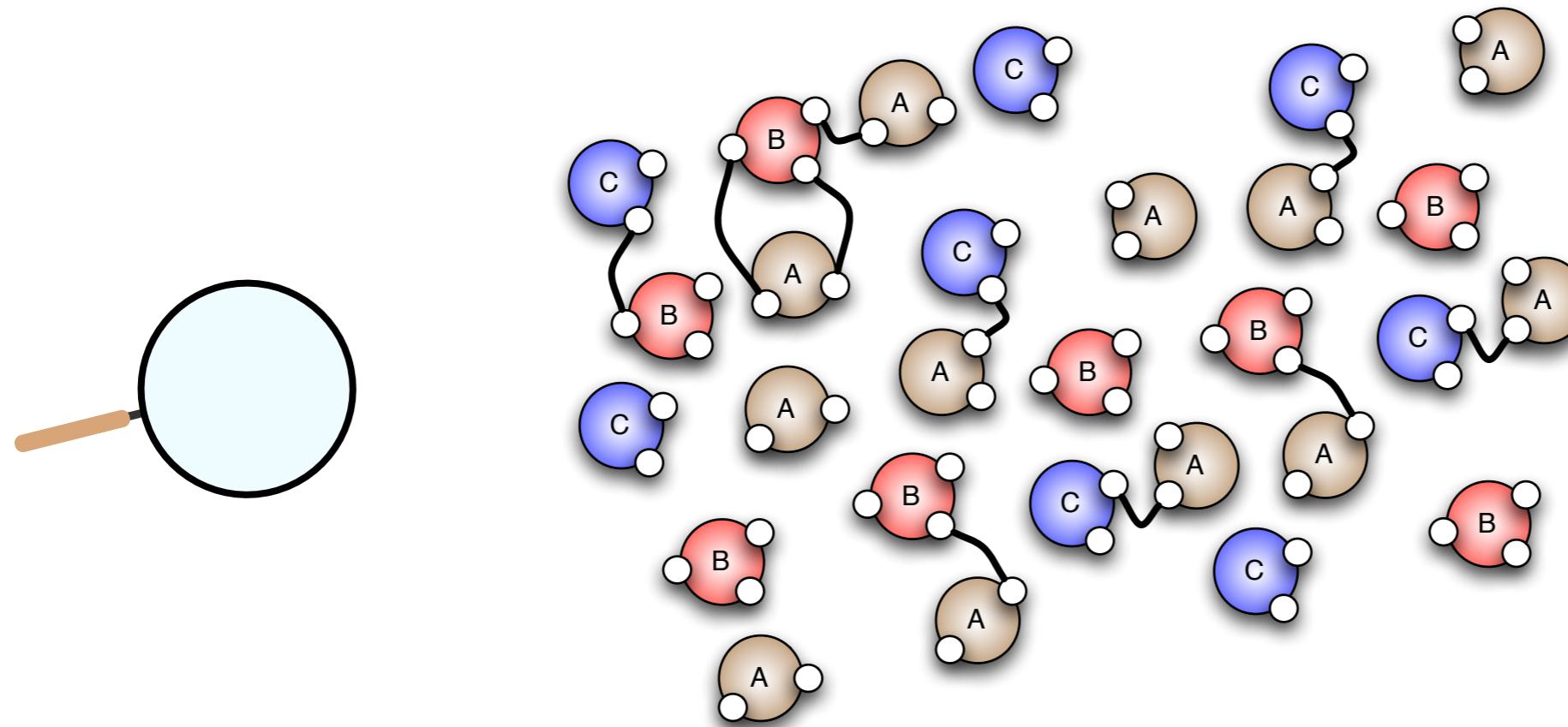
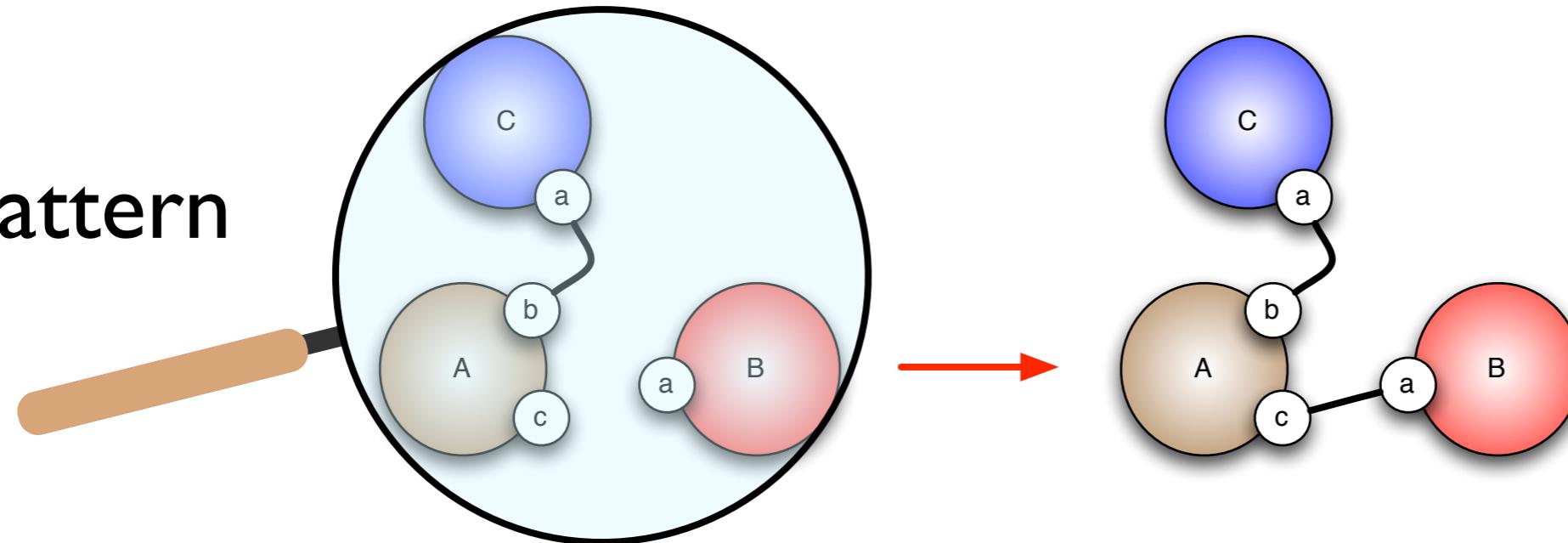
Rule application

A pattern



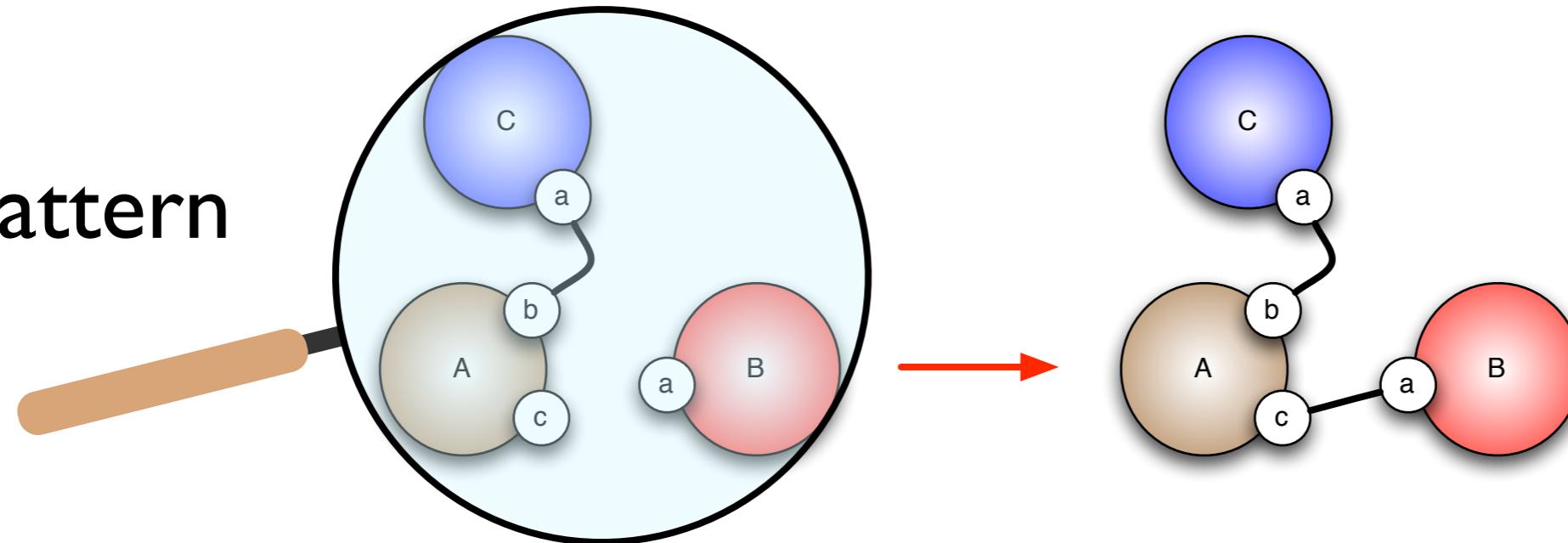
Rule application

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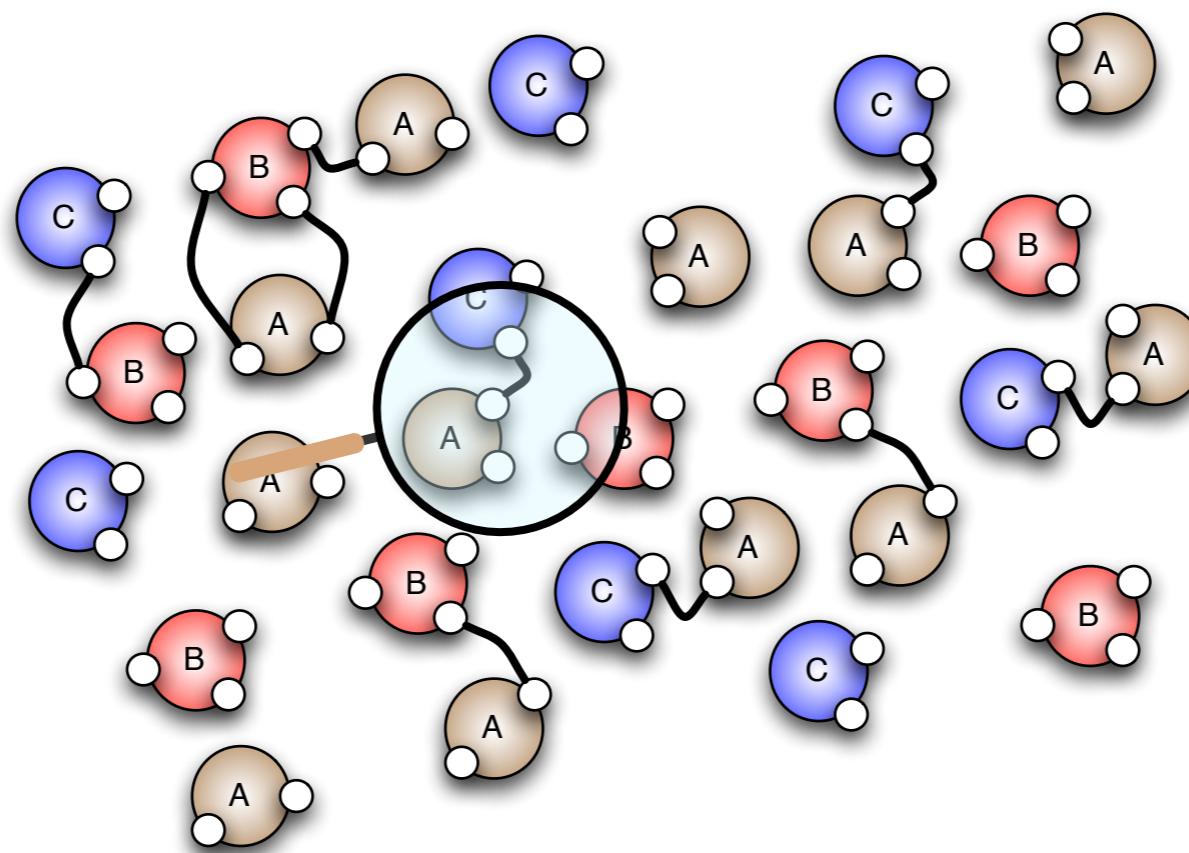


Rule application

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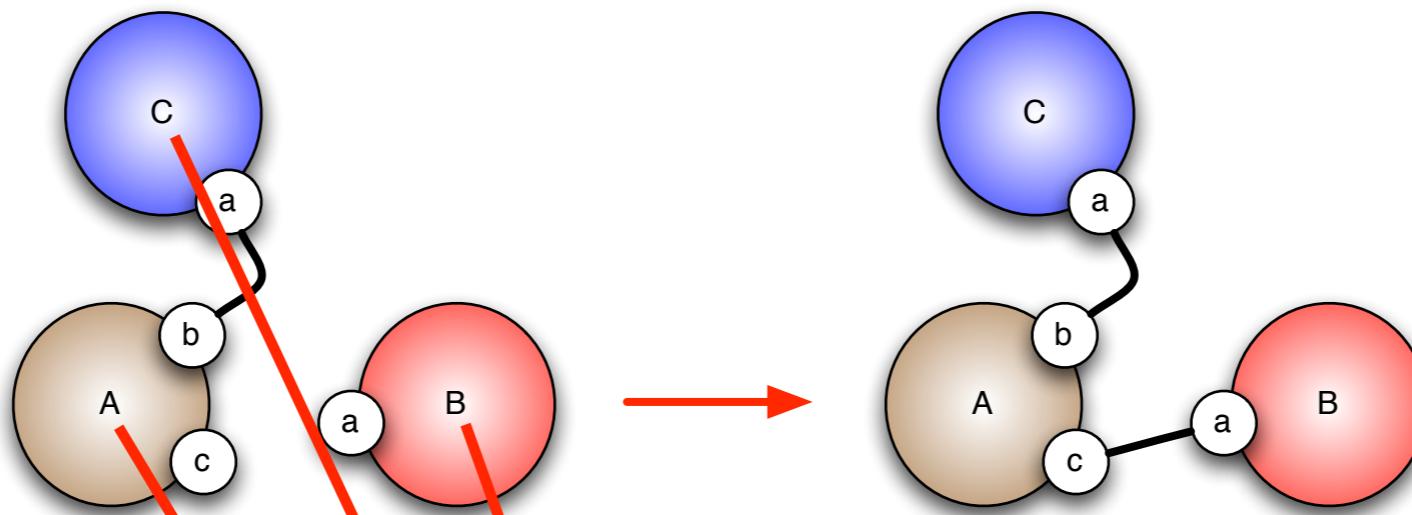


an
instance:

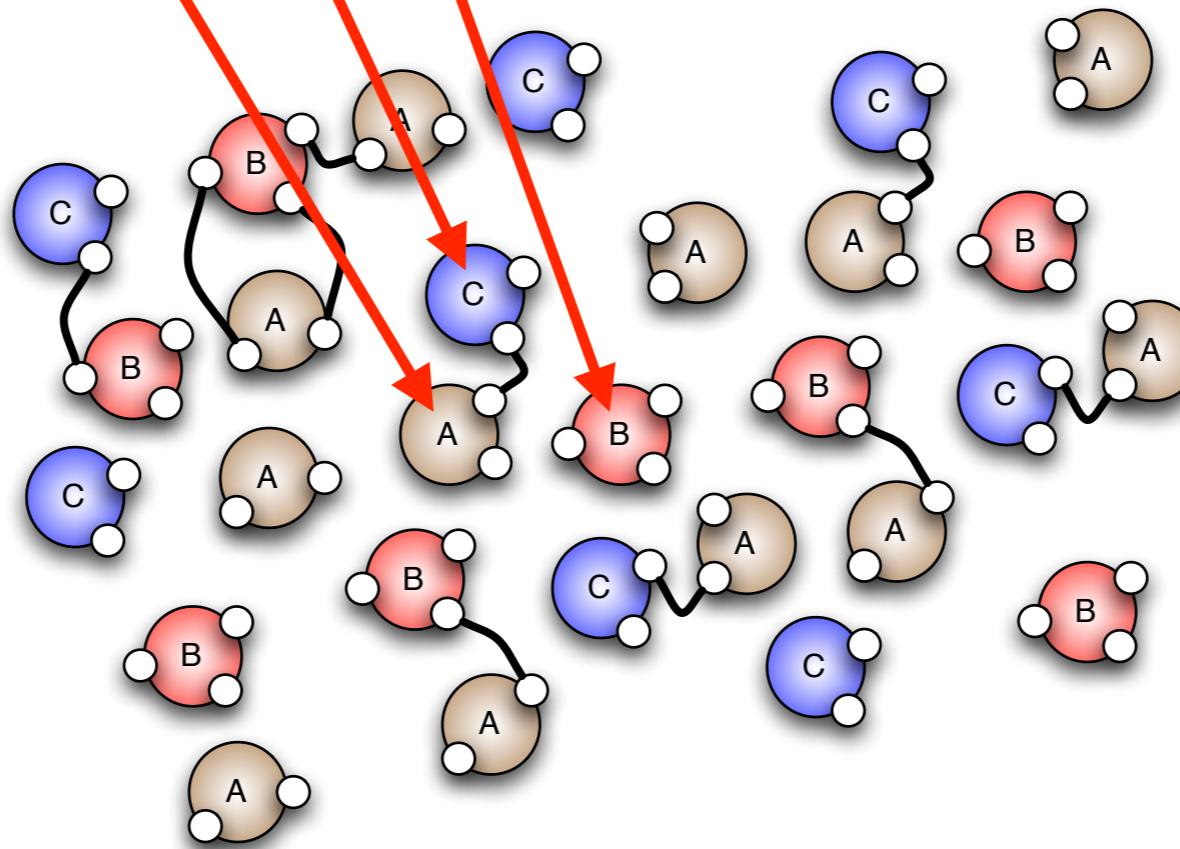


Rule application

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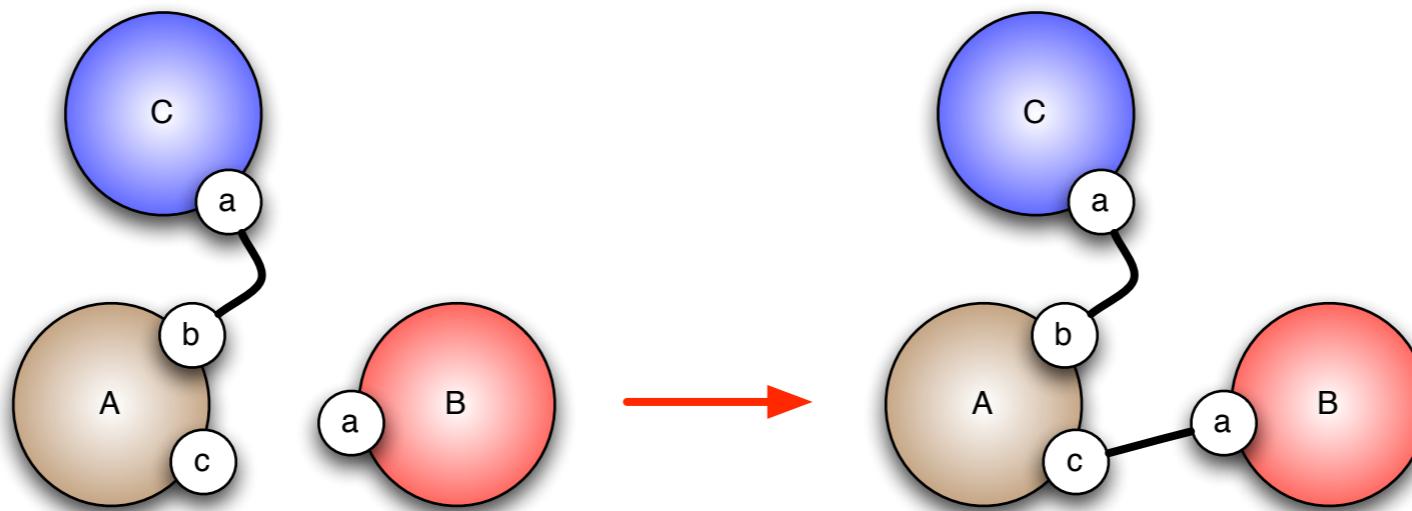


an
instance:

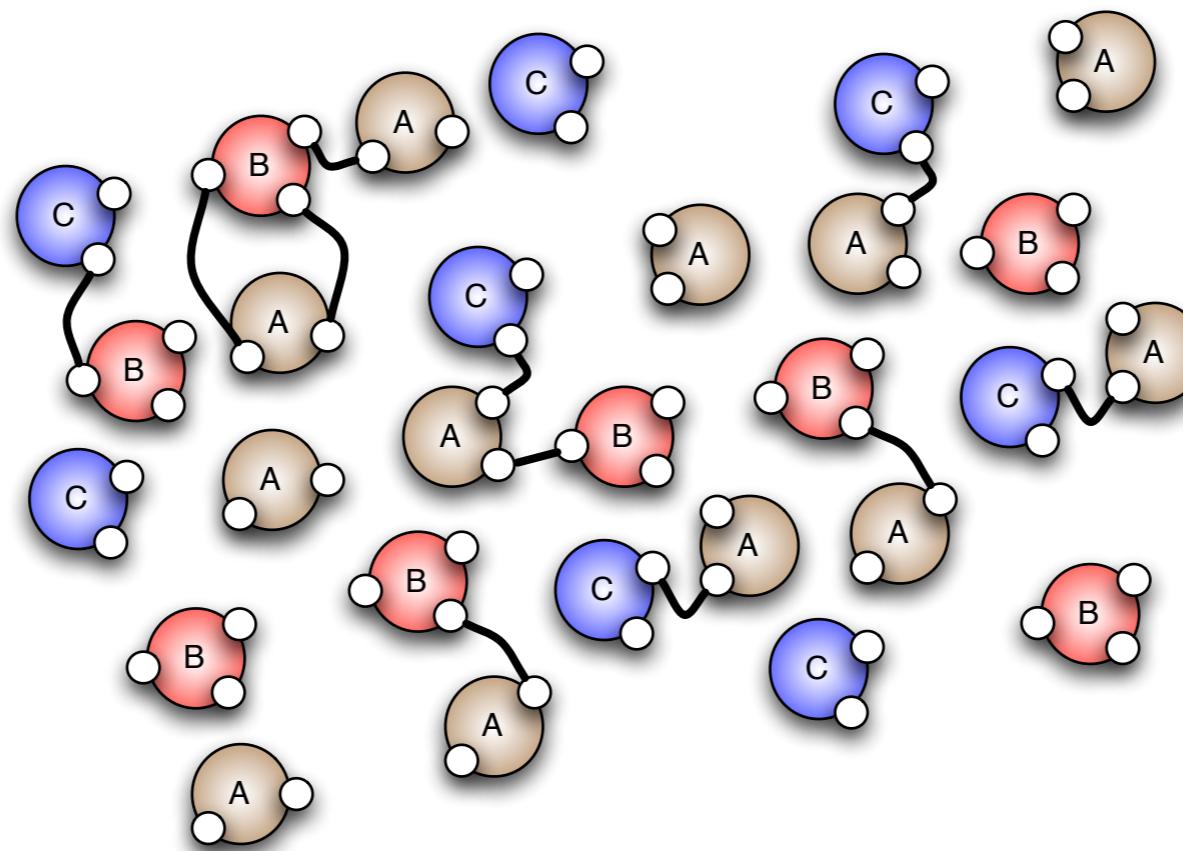


Rule application

A pattern



an
instance:

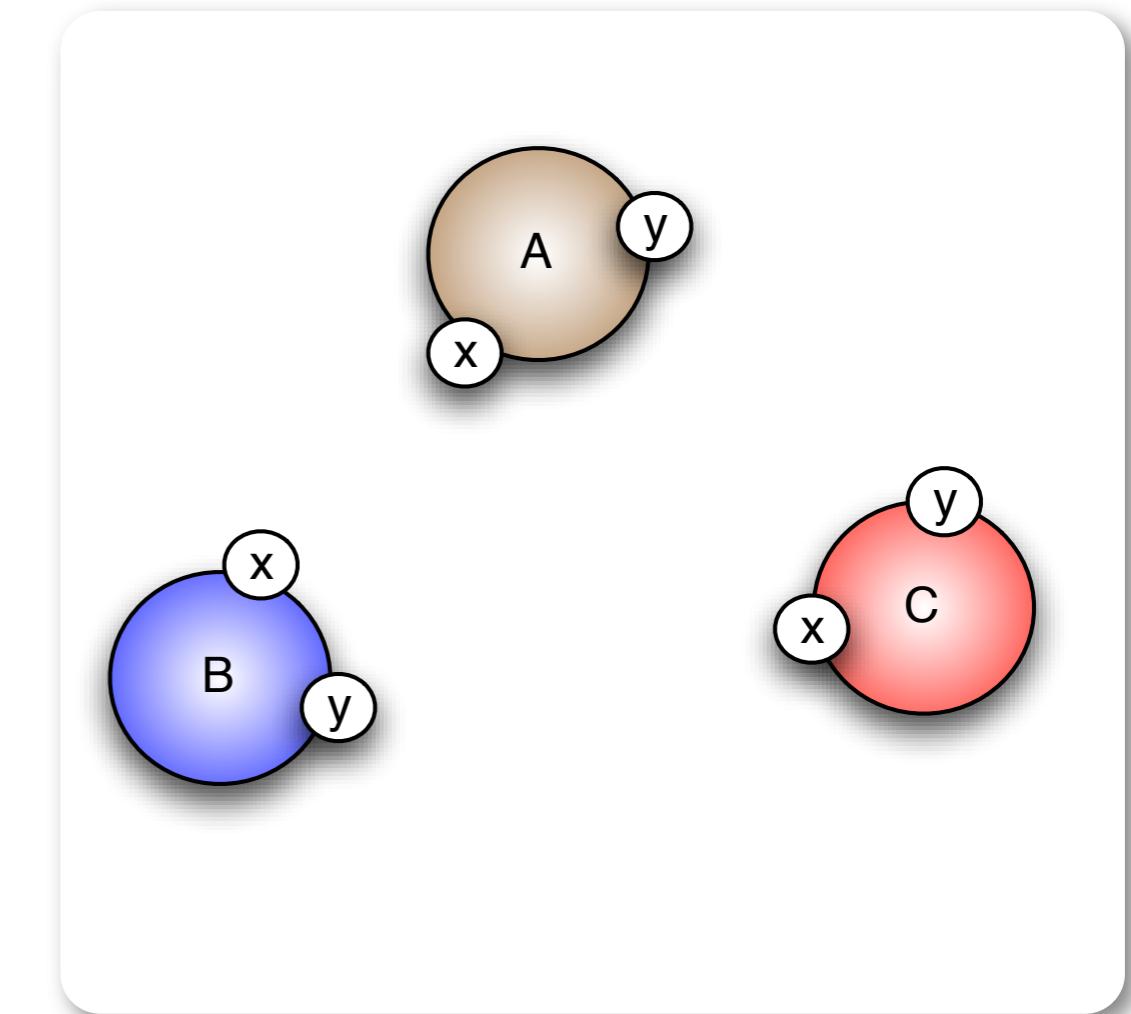


Syntax...

$A(x^1, y^2), B(x^1, y^3), C(x^3, y^2)$

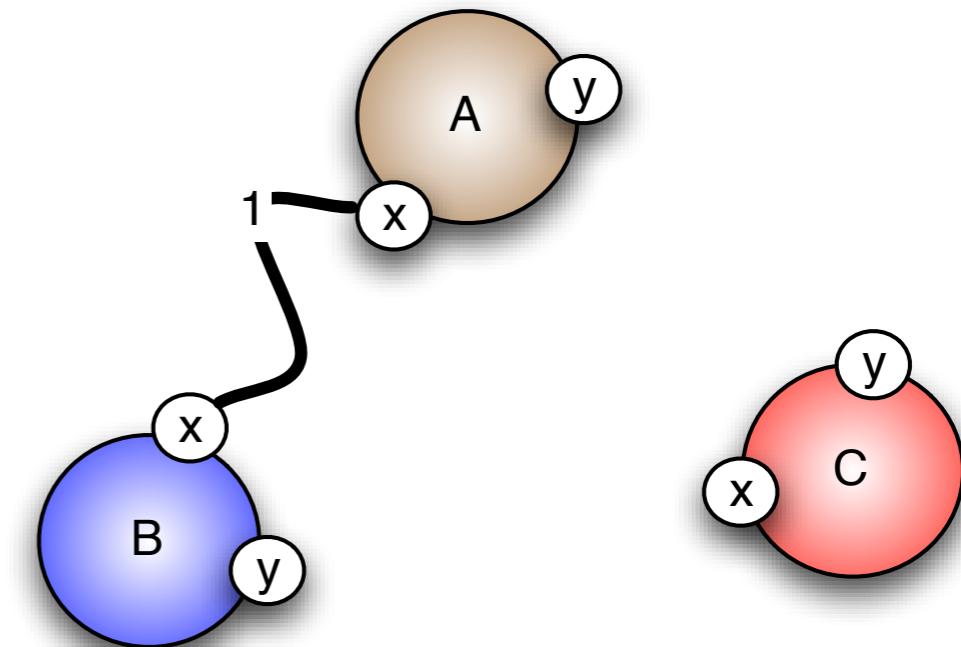
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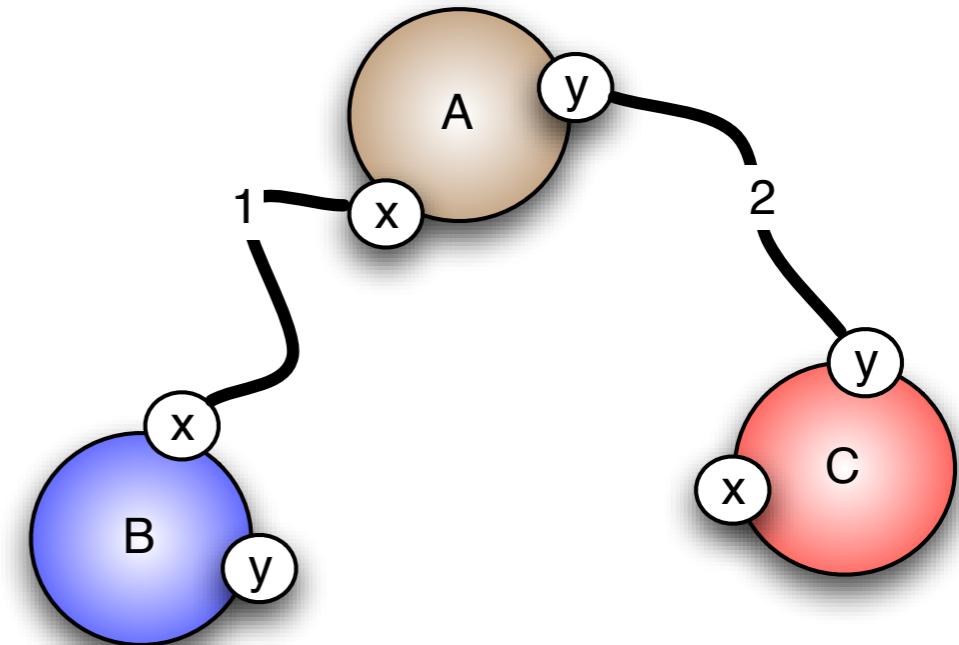
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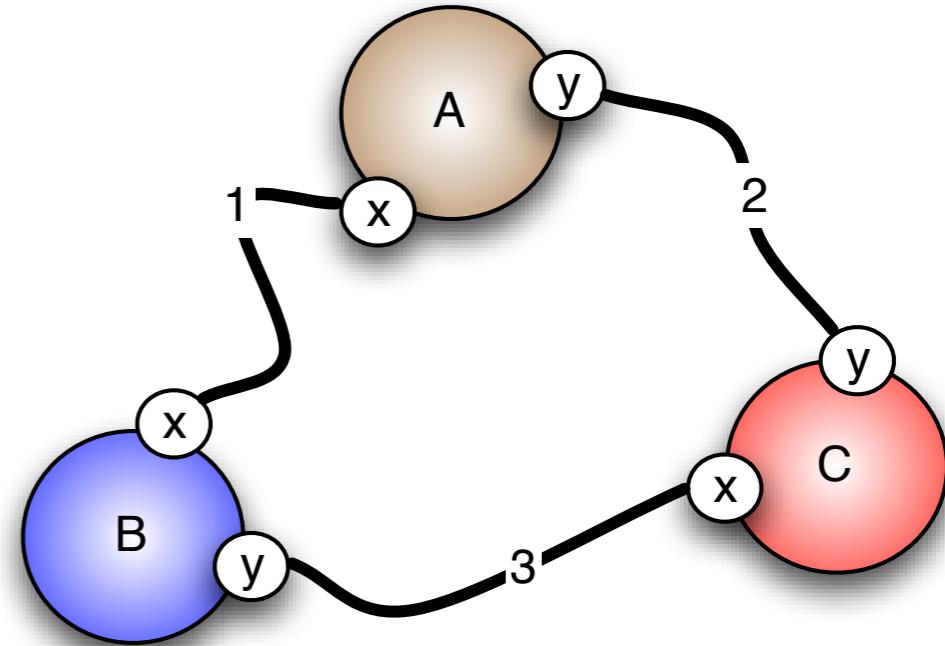
Syntax...

$A(x^1, y^{\textcircled{2}}), B(x^1, y^3), C(x^3, y^{\textcircled{2}})$



Syntax...

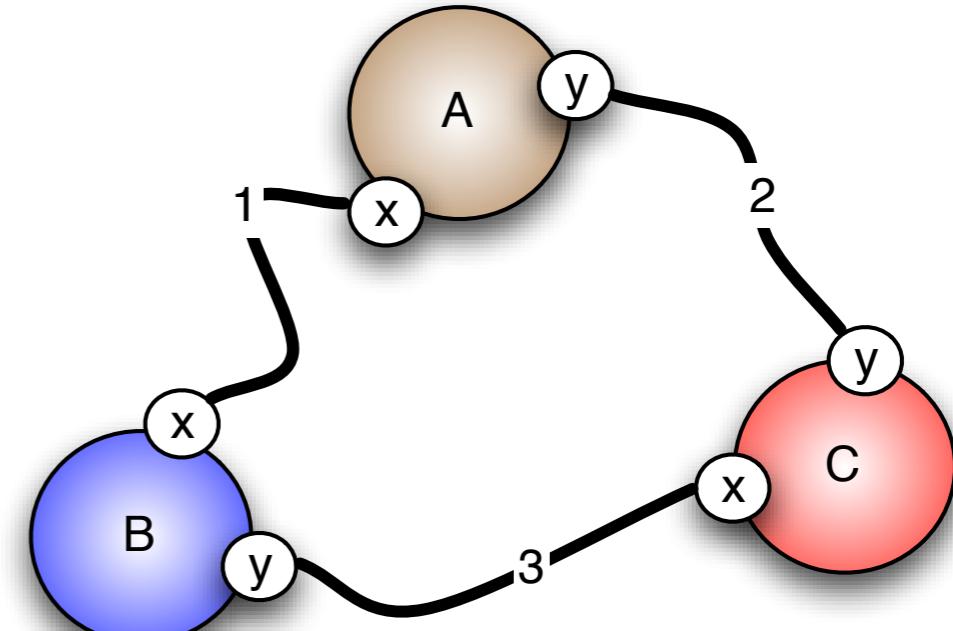
$A(x^1, y^2), B(x^1, y^3), C(x^3, y^2)$



Syntax...

$$A(x^1, y^2), B(x^1, y^3), C(x^3, y^2)$$

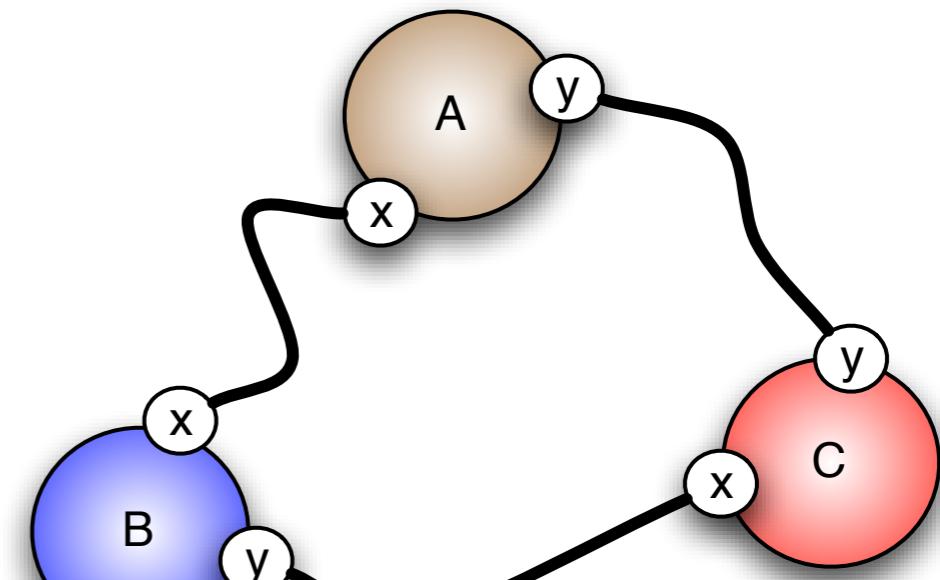
=

$$A(y^0, x^{101}), C(x^{78}, y^0), B(y^{78}, x^{101})$$


Syntax...

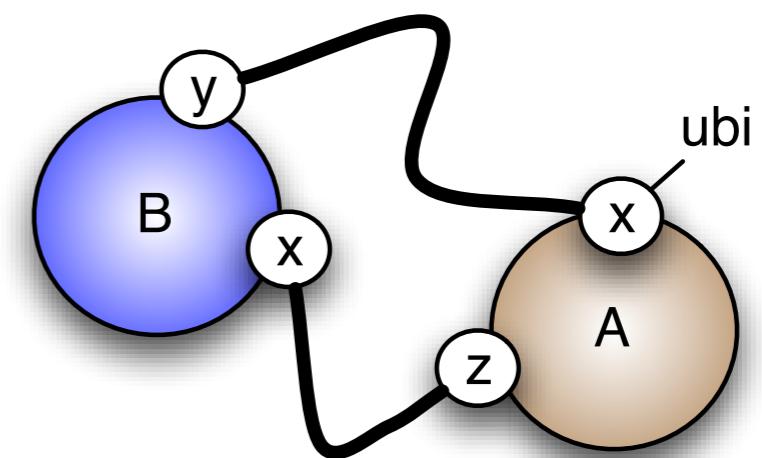
$$A(x^1, y^2), B(x^1, y^3), C(x^3, y^2)$$

=

$$A(y^0, x^{101}), C(x^{78}, y^0), B(y^{78}, x^{101})$$


Syntax...

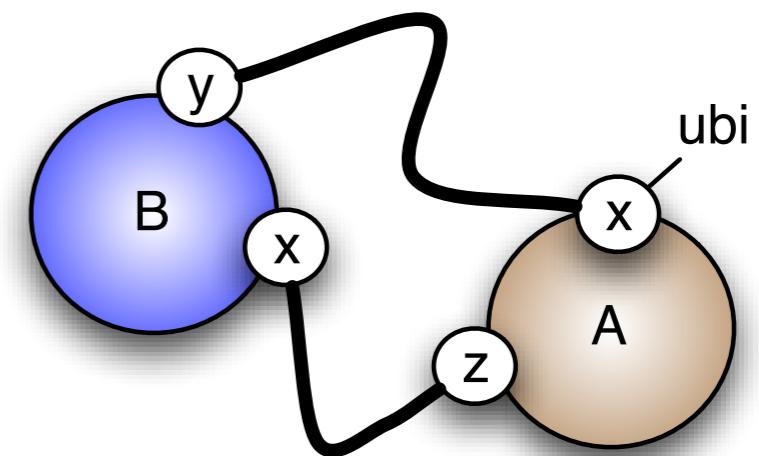
$A(x^1, y^2), B(x^1, y^3), C(x^3, y^2)$



Syntax...

$A(x^1, y^2), B(x^1, y^3), C(x^3, y^2)$

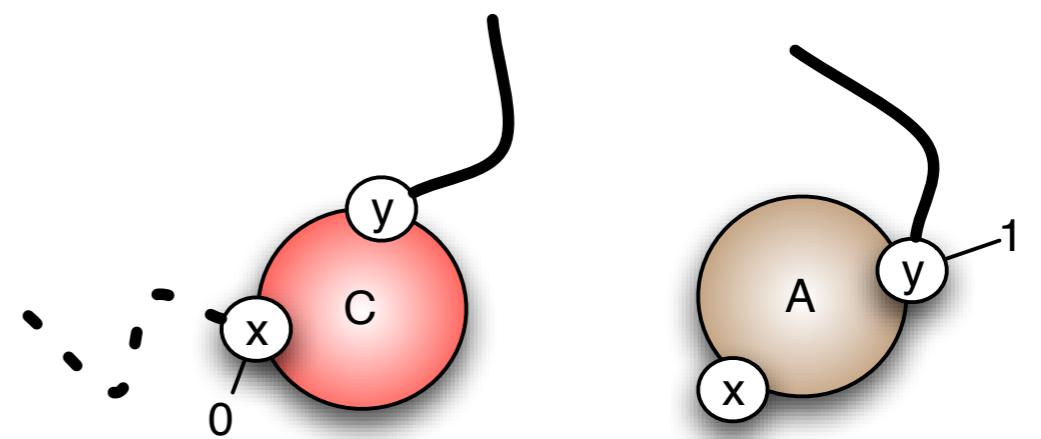
$B(x^1, y^0), A(x_{\text{ubi}}^0, z^1)$



Syntax...

$A(x^1, y^2), B(x^1, y^3), C(x^3, y^2)$

$B(x^1, y^0), A(x_{\text{ubi}}^0, z^1)$

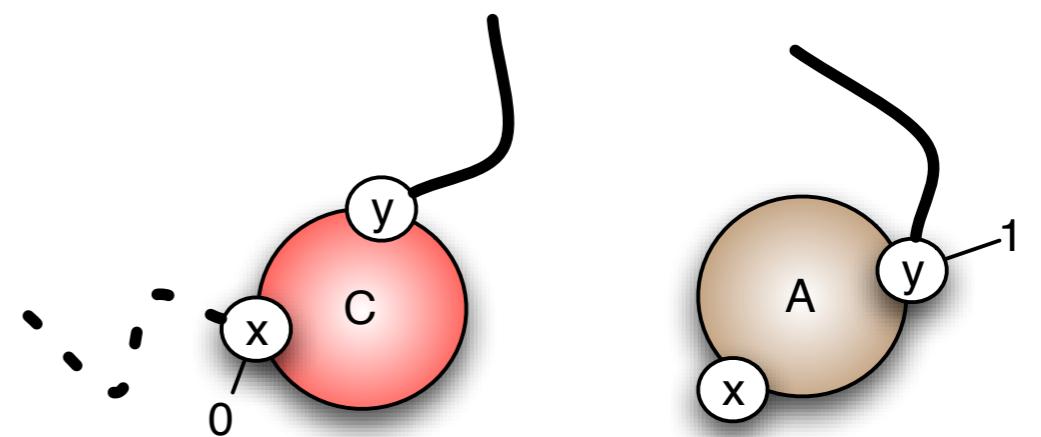


Syntax...

$A(x^1, y^2), B(x^1, y^3), C(x^3, y^2)$

$B(x^1, y^0), A(x_{\text{ubi}}^0, z^1)$

$A(x_0^?, y^-), C(x, y_1^-)$

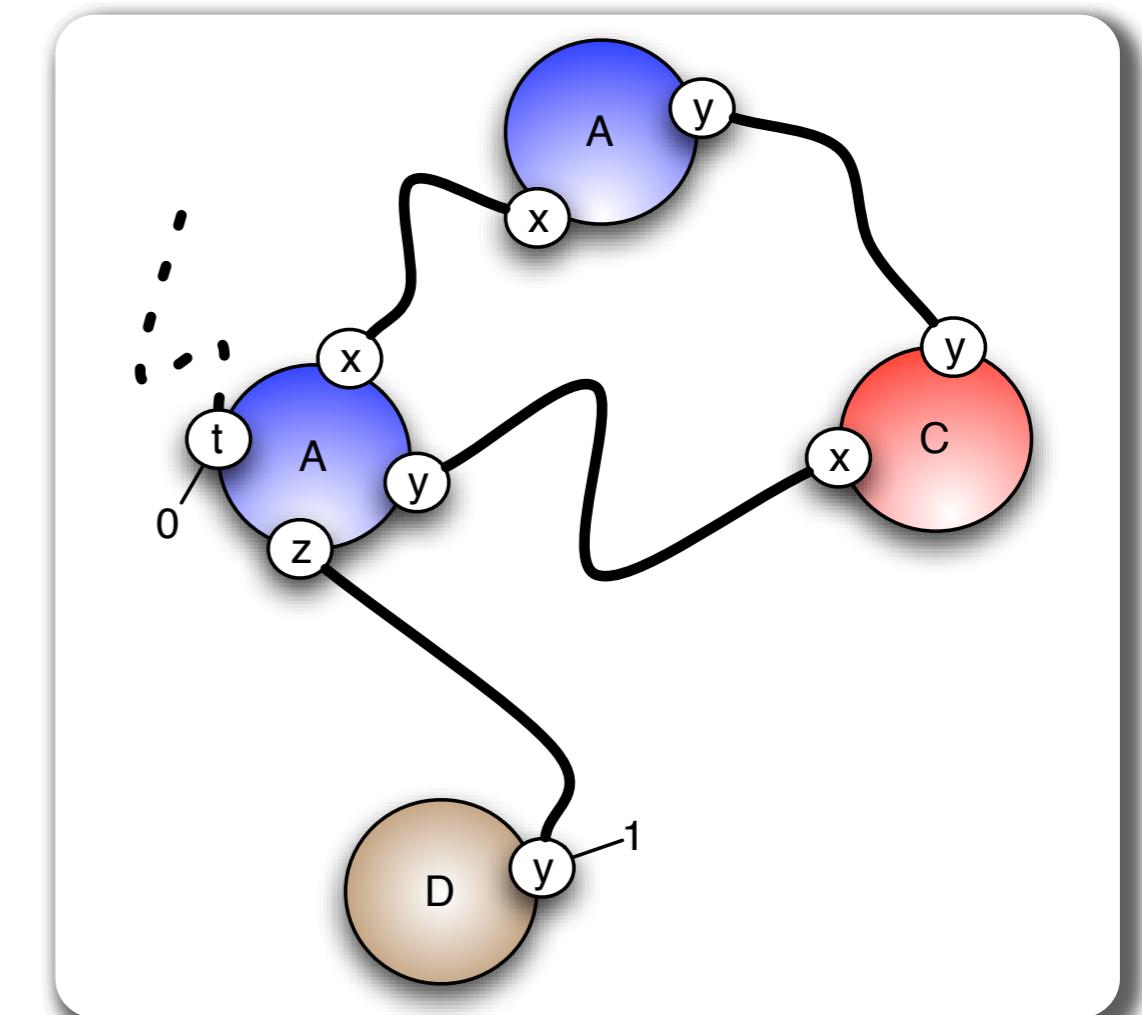


Syntax...

$A(x^1, y^2), B(x^1, y^3), C(x^3, y^2)$

$B(x^1, y^0), A(x_0^0, z^1)$

$A(x_0^?, y^-), C(x, y_1^-)$



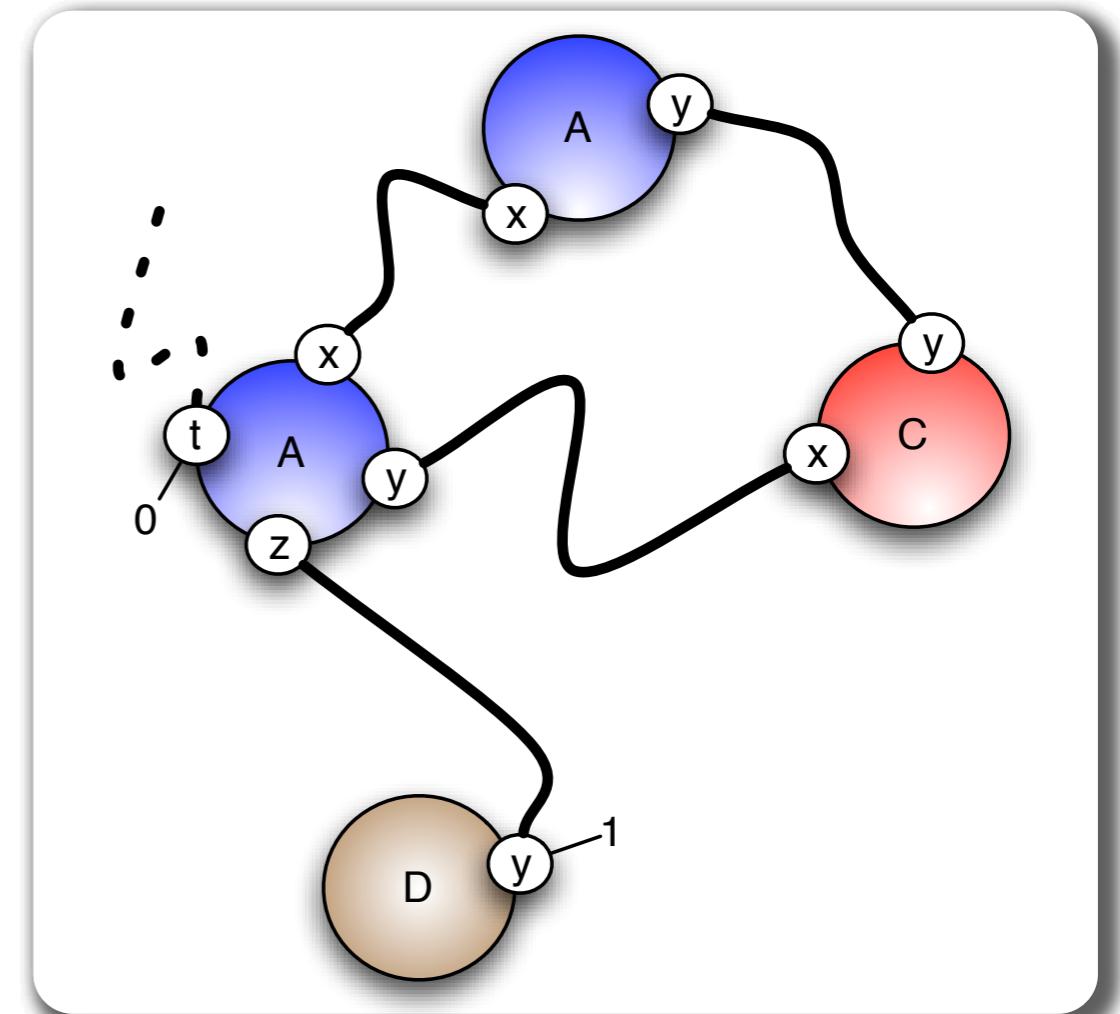
Syntax...

$A(x^1, y^2), B(x^1, y^3), C(x^3, y^2)$

$B(x^1, y^0), A(x_0^0, z^1)$

$A(\dot{x}_0, y^-), C(x, y_1^-)$

$A(x^1, y^2), A(x^1, y^3, z^4, t_0^?), C(x^3, y^2), D(y_1^4)$



Pattern matching

Definition [Embedding]

A map φ between solutions S and T is an *embedding* if for all $a, b \in S$:

$$\varphi(a) = \varphi(b) \Rightarrow a = b$$

$$\text{Name}_S(a) = \text{Name}_T(\varphi(a))$$

$$\text{Sites}_S(a) \subseteq \text{Sites}_T(\varphi(a))$$

$$\text{Link}_S(a, x) = (b, y) \Rightarrow \text{Link}_T(\varphi(a), x) = (\varphi(b), y)$$

$$x_\iota^\lambda \in \text{Sites}_S(a) \Rightarrow x_{\iota'}^{\lambda'} \in \text{Sites}_T(\varphi(a)) \text{ with } \iota \leq \iota', \lambda \leq \lambda'$$

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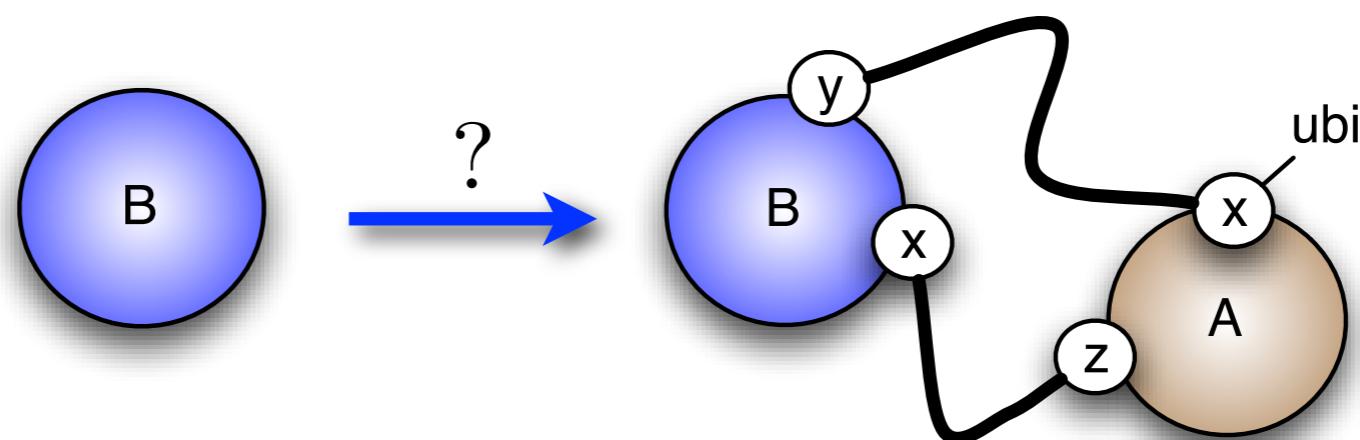
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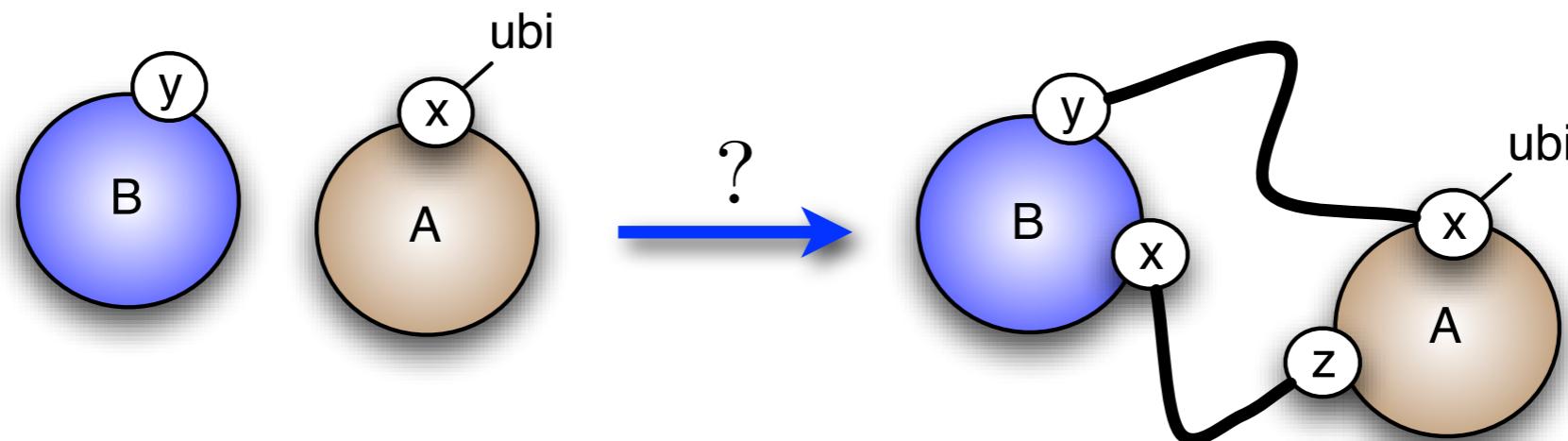
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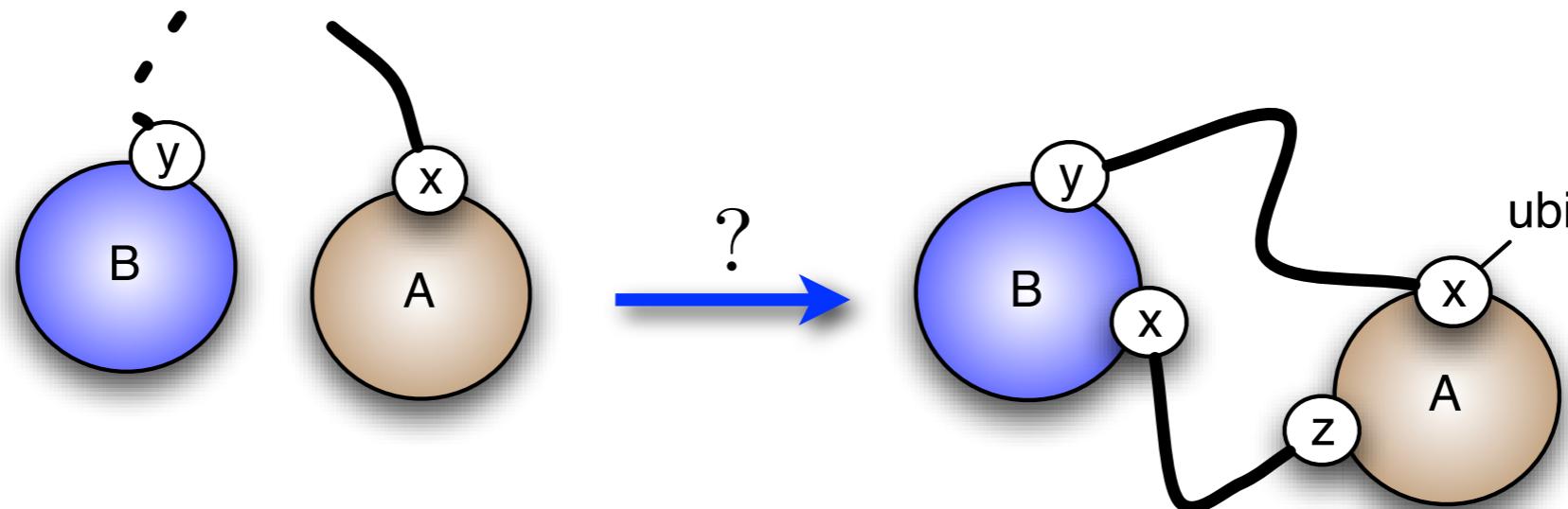
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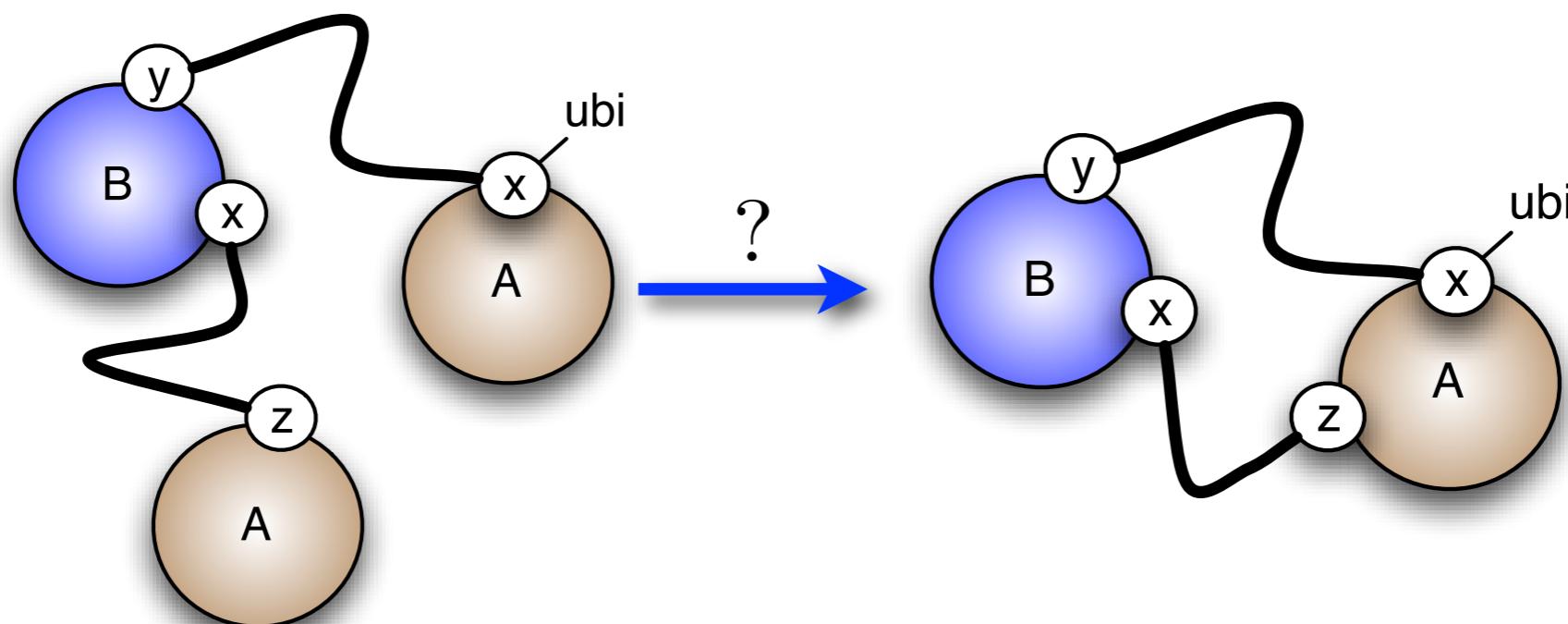
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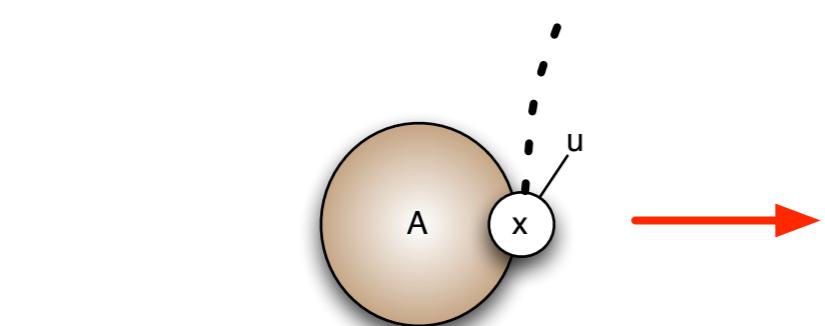
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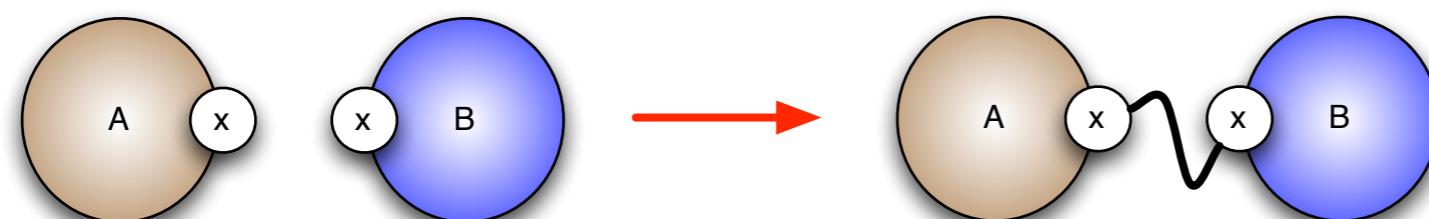
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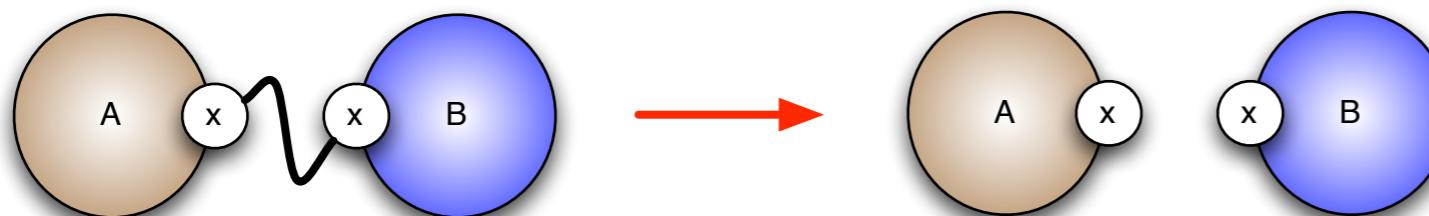
Elementary actions



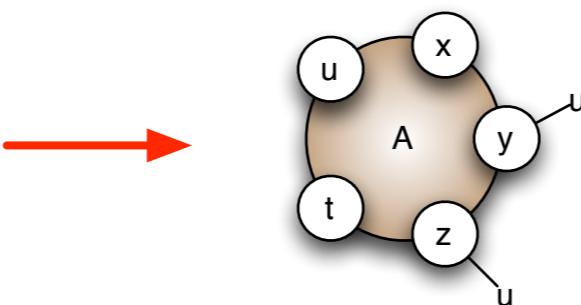
Modification



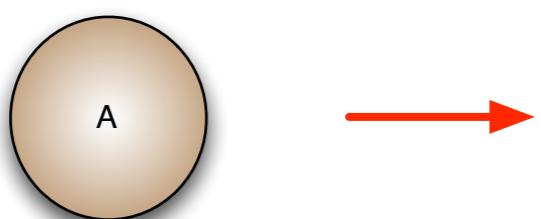
Binding



Unbinding

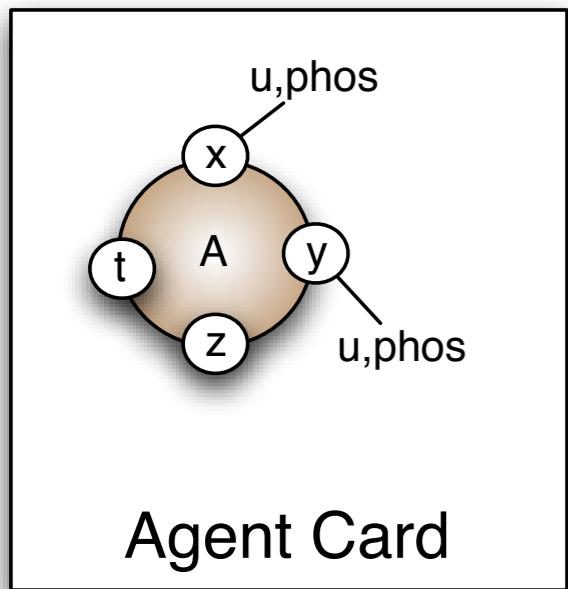


Synthesis

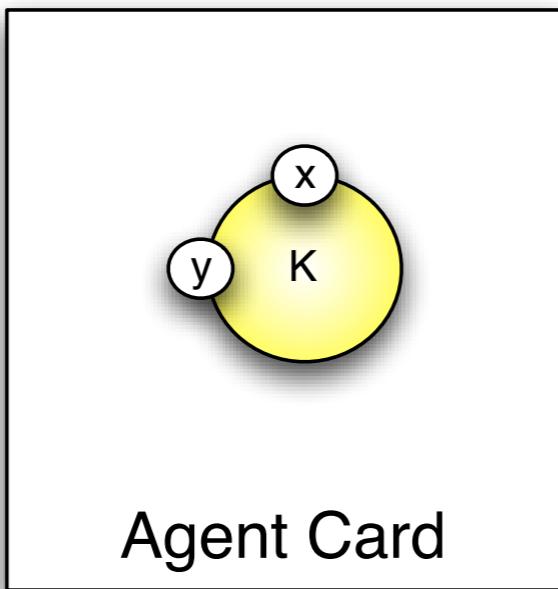


Degradation

Rules



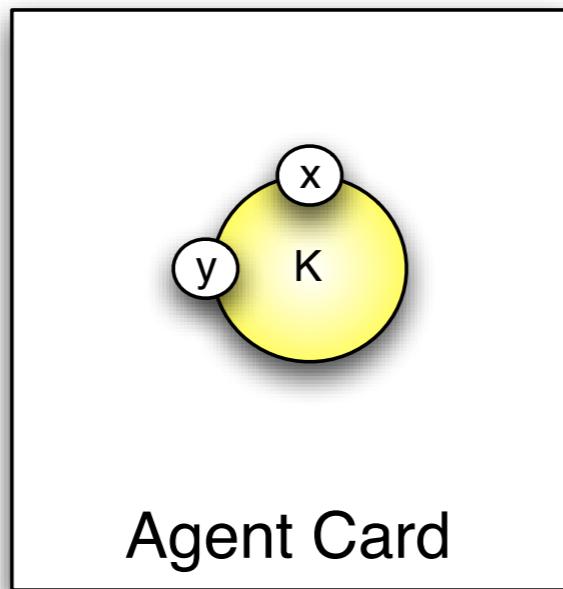
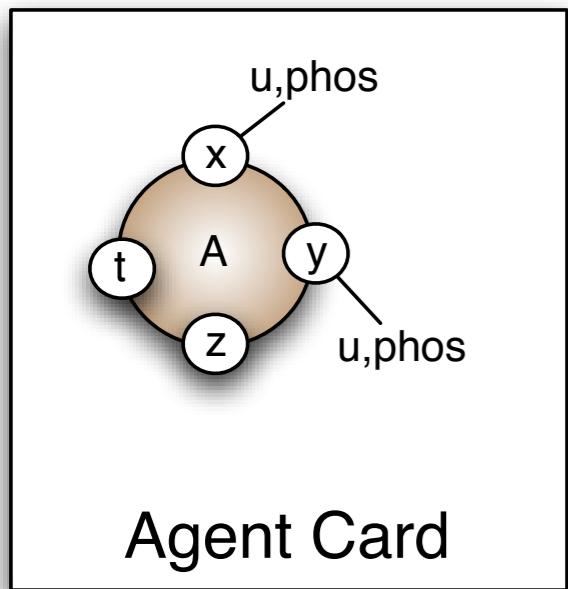
Agent Card



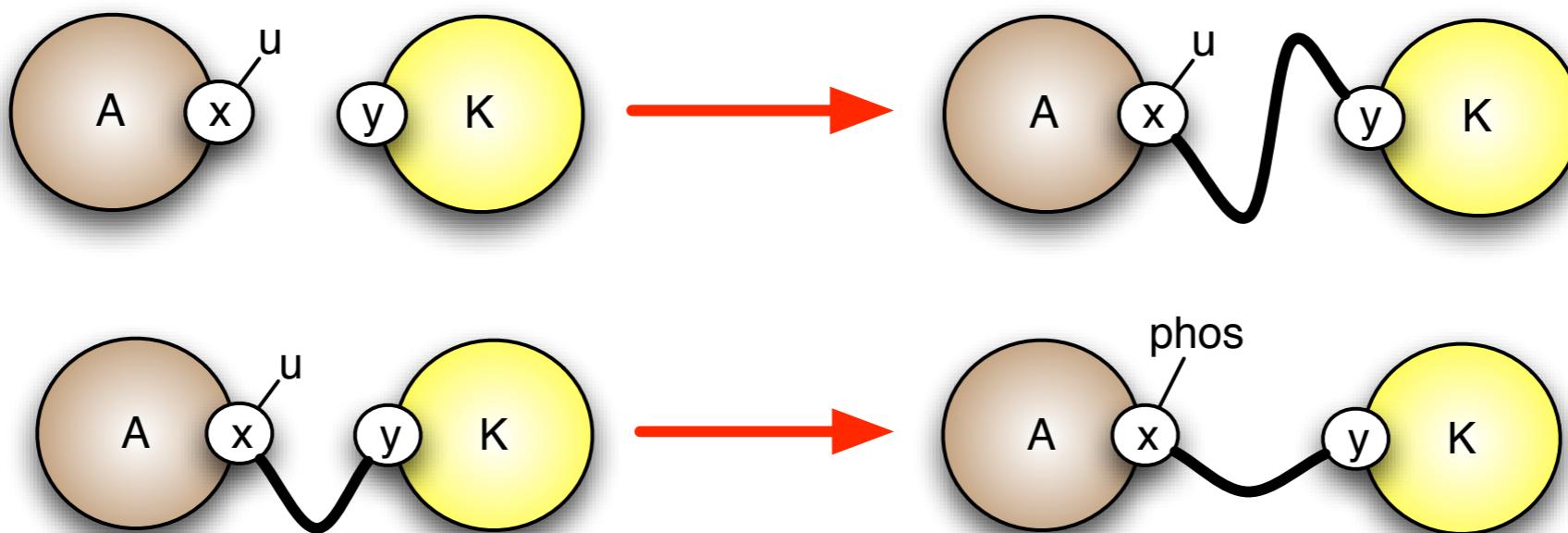
Agent Card

Protein *A* is activated by kinase *K* on site *x*.

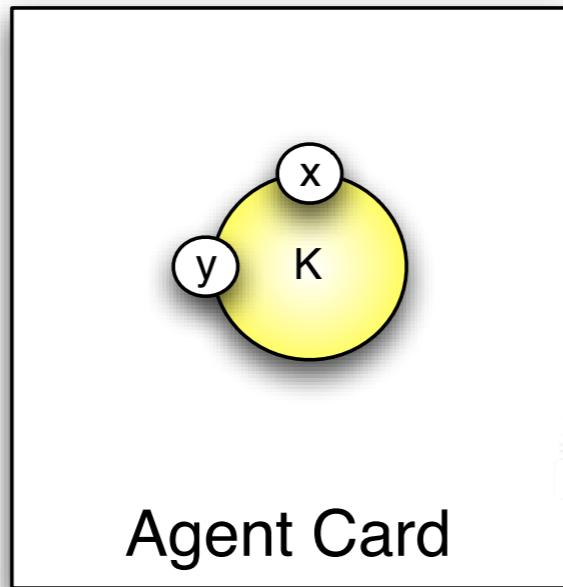
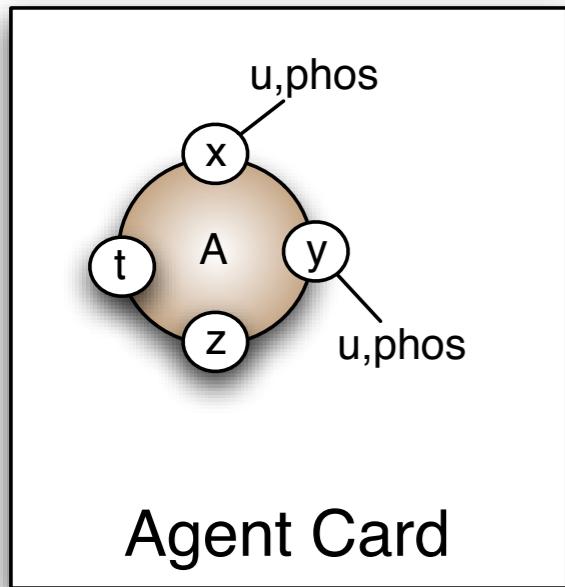
Rules



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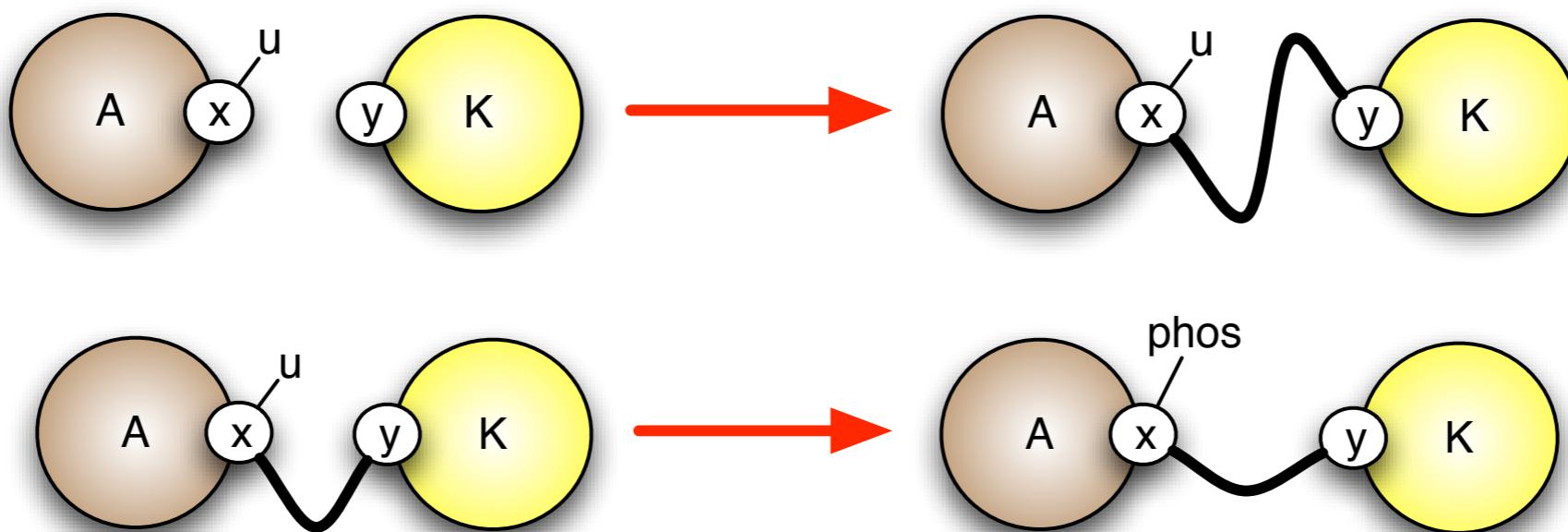


Rules

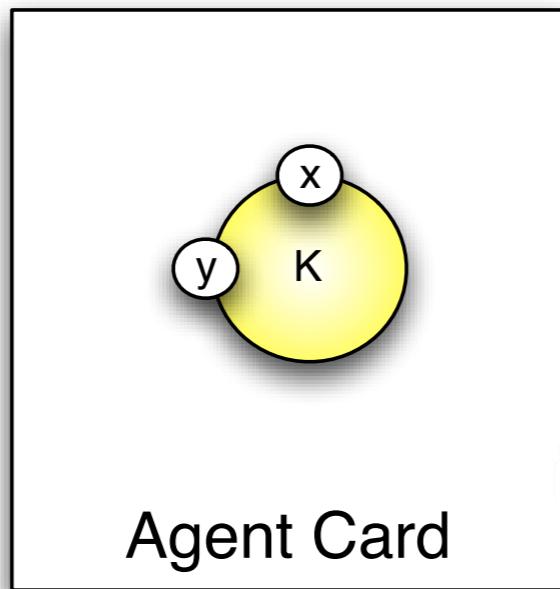
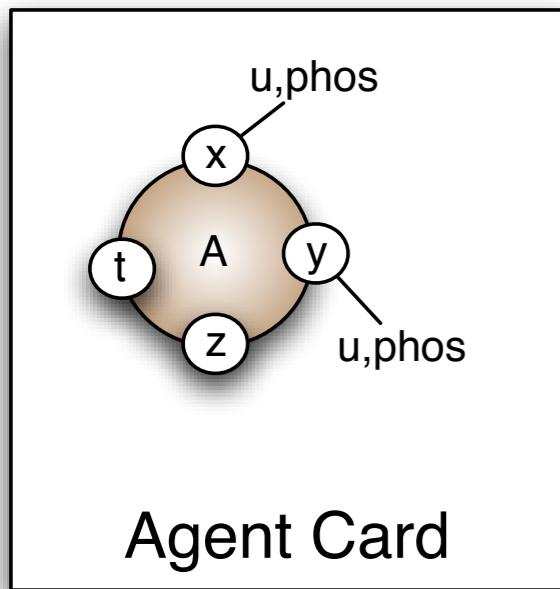


Protein *A* is activated by kinase *K* on site *x*.

Phosphorylated site *y* prevents kinase to activate *x*

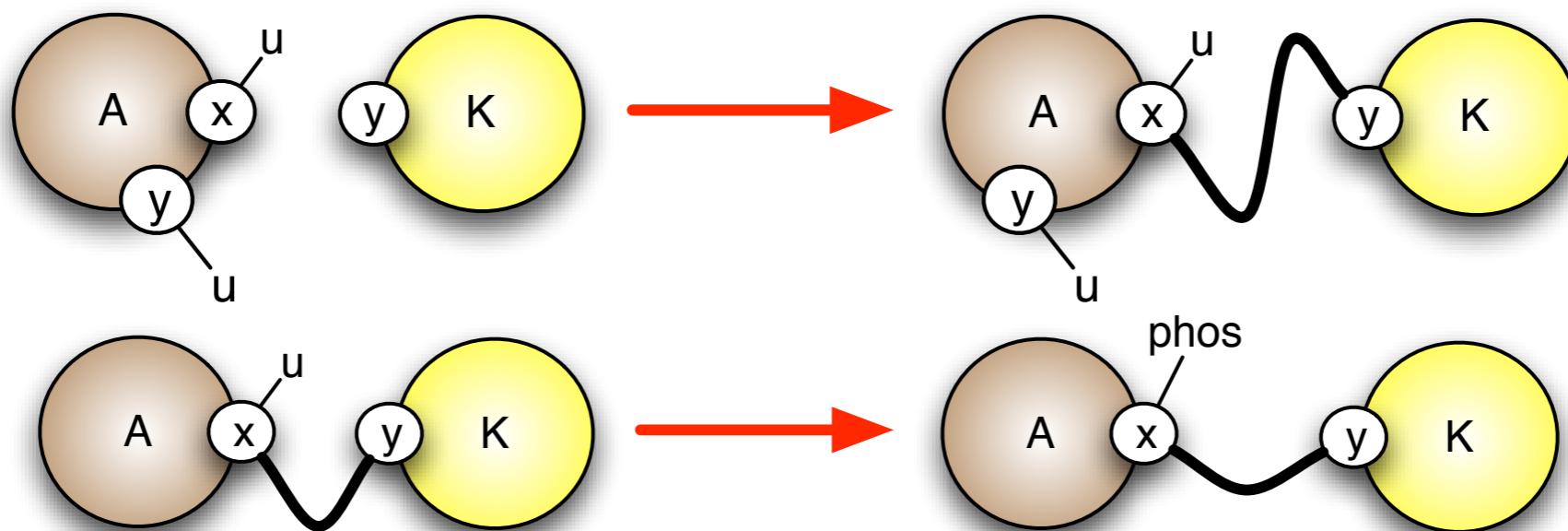


Rules

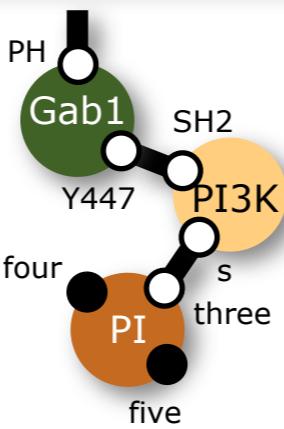
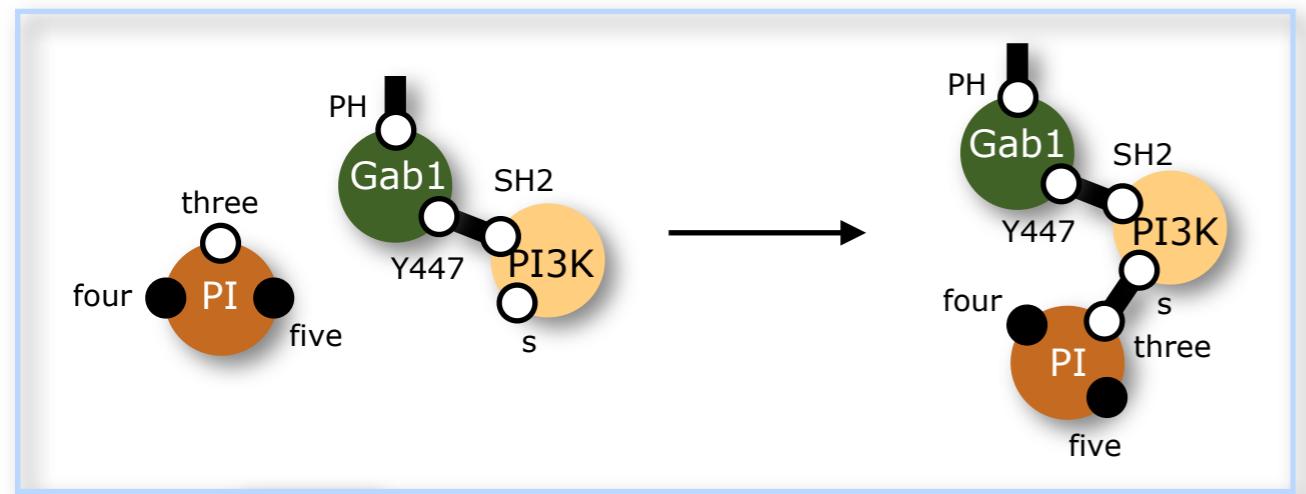


Protein A is activated by kinase K on site x .

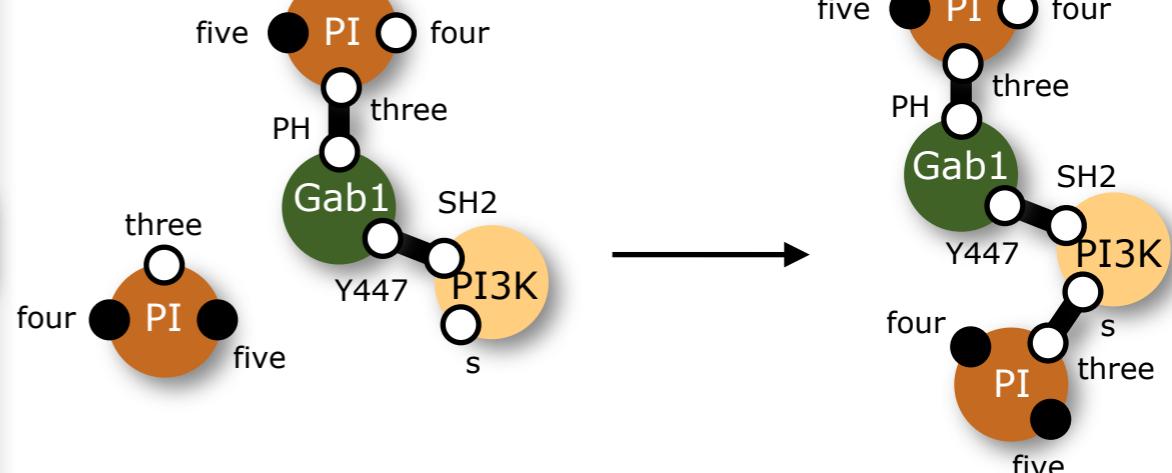
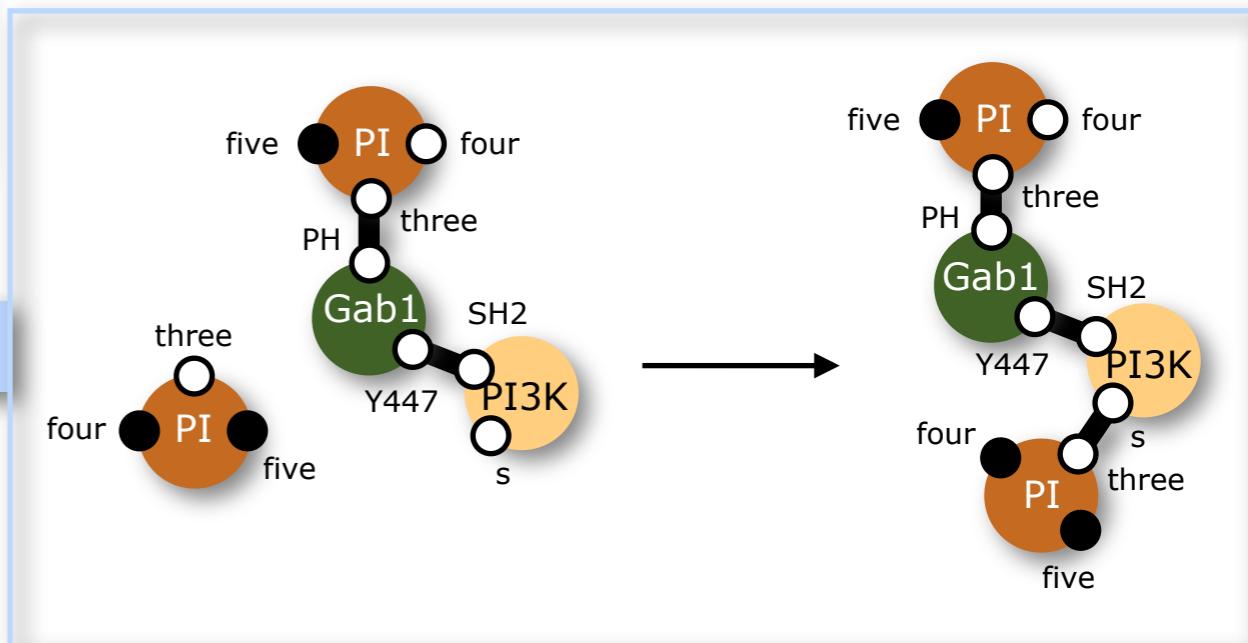
Phosphorylated site y prevents kinase to activate x



rules, instances, events



instance



event

